```
FILE 'HOME' ENTERED AT 07:46:58 ON 18 MAR 2008

=> index bioscience
FILE 'DRUGMONOG' ACCESS NOT AUTHORIZED
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.21       0.21

INDEX 'ADISCTI, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, ANTE, AQUALINE,
       AQUASCI, BIOENG, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CAPLUS,
       CEABA-VTB, CIN, CONFSCI, CROPB, CROPU, DDFB, DDFU, DGENE, DISSABS, DRUGB,
       DRUGMONOG2, DRUGU, EMBAL, EMBASE, ...' ENTERED AT 07:47:36 ON 18 MAR 2008

69 FILES IN THE FILE LIST IN STNINDEX

Enter SET DETAIL ON to see search term postings or to view
search error messages that display as 0* with SET DETAIL OFF.

=> s enzym######## (s) (multipl##### or plural### or dual or simultaneous## or
combin##)
        265   FILE ADISCTI
        391   FILE ADISINSIGHT
        330   FILE ADISNEWS
       4172   FILE AGRICOLA
       1687   FILE ANABSTR
        203   FILE ANTE
        239   FILE AQUALINE
       1374   FILE AQUASCI
       5659   FILE BIOENG
      17920   FILE BIOSIS
       8557   FILE BIOTECHABS
       8557   FILE BIOTECHDS
      18519   FILE BIOTECHNO
       9913   FILE CABA
      27218   FILE CAPLUS
       1367   FILE CEABA-VTB
        180   FILE CIN
        147   FILE CONFSCI
  18 FILES SEARCHED...
         19   FILE CROPB
        254   FILE CROPU
        144   FILE DDFB
       1995   FILE DDFU
      58063   FILE DGENE
       3455   FILE DISSABS
        144   FILE DRUGB
         21   FILE DRUGMONOG2
       4524   FILE DRUGU
        139   FILE EMBAL
      13735   FILE EMBASE
      25305   FILE ESBIOBASE
  30 FILES SEARCHED...
          4   FILE FOMAD
          1   FILE FOREGE
       1237   FILE FROSTI
       3011   FILE FSTA
     384422   FILE GENBANK
        186   FILE HEALSAFE
       6556   FILE IFIPAT
         92   FILE IMSDRUGNEWS
          1   FILE IMSPRODUCT
```

```
       160   FILE IMSRESEARCH
       181   FILE KOSMET
     19642   FILE LIFESCI
     14985   FILE MEDLINE
       626   FILE NTIS
        14   FILE NUTRACEUT
       323   FILE OCEAN
     18836   FILE PASCAL
        16   FILE PHAR
  49 FILES SEARCHED...
        50   FILE PHARMAML
         1   FILE PHIC
       350   FILE PHIN
      3174   FILE PROMT
       600   FILE PROUSDDR
        49   FILE RDISCLOSURE
     12819   FILE SCISEARCH
        12   FILE SYNTHLINE
      8709   FILE TOXCENTER
      9348   FILE USGENE
     69433   FILE USPATFULL
      1290   FILE USPATOLD
     10357   FILE USPAT2
         1   FILE VETB
       170   FILE VETU
       368   FILE WATER
      6617   FILE WPIDS
  67 FILES SEARCHED...
       128   FILE WPIFV
      6617   FILE WPINDEX

  67 FILES HAVE ONE OR MORE ANSWERS,   69 FILES SEARCHED IN STNINDEX

L1   QUE ENZYM######## (S) (MULTIPL##### OR PLURAL### OR DUAL OR SIMULTANEOUS##
         OR COMBIN##)

=> s L1 (s) (activat### or assay### or detect### or quantif#### or measur###)
        38   FILE ADISCTI
       137   FILE ADISINSIGHT
        85   FILE ADISNEWS
      1653   FILE AGRICOLA
      1125   FILE ANABSTR
        65   FILE ANTE
       124   FILE AQUALINE
       542   FILE AQUASCI
      2167   FILE BIOENG
      2827   FILE BIOSIS
      3998   FILE BIOTECHABS
      3998   FILE BIOTECHDS
      9548   FILE BIOTECHNO
  13 FILES SEARCHED...
      4050   FILE CABA
      3857   FILE CAPLUS
       300   FILE CEABA-VTB
        16   FILE CIN
        21   FILE CONFSCI
        71   FILE CROPU
         7   FILE DDFB
       405   FILE DDFU
     15948   FILE DGENE
  23 FILES SEARCHED...
```

```
      1347   FILE DISSABS
         7   FILE DRUGB
      1375   FILE DRUGU
        20   FILE EMBAL
      2324   FILE EMBASE
     11998   FILE ESBIOBASE
       312   FILE FROSTI
       825   FILE FSTA
       603   FILE GENBANK
  35 FILES SEARCHED...
        89   FILE HEALSAFE
      3030   FILE IFIPAT
        23   FILE IMSDRUGNEWS
        60   FILE IMSRESEARCH
        67   FILE KOSMET
      8293   FILE LIFESCI
      2568   FILE MEDLINE
       238   FILE NTIS
       134   FILE OCEAN
      8875   FILE PASCAL
  47 FILES SEARCHED...
         1   FILE PHAR
         9   FILE PHARMAML
        92   FILE PHIN
       709   FILE PROMT
        30   FILE PROUSDDR
         9   FILE RDISCLOSURE
      2260   FILE SCISEARCH
      1296   FILE TOXCENTER
      3823   FILE USGENE
     26900   FILE USPATFULL
  61 FILES SEARCHED...
       199   FILE USPATOLD
      4084   FILE USPAT2
        58   FILE VETU
       194   FILE WATER
      2298   FILE WPIDS
        43   FILE WPIFV
  68 FILES SEARCHED...
      2298   FILE WPINDEX

  58 FILES HAVE ONE OR MORE ANSWERS,   69 FILES SEARCHED IN STNINDEX

L2   QUE L1 (S) (ACTIVAT### OR ASSAY### OR DETECT### OR QUANTIF#### OR MEASUR##
        #)

=> s L2 (s) (luminesc##### or luminos###)
         4   FILE AGRICOLA
        16   FILE ANABSTR
         3   FILE AQUASCI
        10   FILE BIOENG
         6   FILE BIOSIS
       113   FILE BIOTECHABS
       113   FILE BIOTECHDS
        26   FILE BIOTECHNO
  13 FILES SEARCHED...
         4   FILE CABA
        24   FILE CAPLUS
         6   FILE CEABA-VTB
        27   FILE DGENE
  23 FILES SEARCHED...
```

```
          3   FILE DISSABS
          2   FILE DRUGU
          6   FILE EMBASE
         21   FILE ESBIOBASE
          3   FILE FROSTI
          4   FILE FSTA
         14   FILE GENBANK
  36 FILES SEARCHED...
         64   FILE IFIPAT
         20   FILE LIFESCI
          7   FILE MEDLINE
          3   FILE NTIS
         25   FILE PASCAL
  47 FILES SEARCHED...
          1   FILE PHIN
          7   FILE PROMT
          9   FILE SCISEARCH
          3   FILE TOXCENTER
        194   FILE USGENE
        765   FILE USPATFULL
        103   FILE USPAT2
  64 FILES SEARCHED...
          1   FILE WATER
         82   FILE WPIDS
          1   FILE WPIFV
         82   FILE WPINDEX

  35 FILES HAVE ONE OR MORE ANSWERS,   69 FILES SEARCHED IN STNINDEX

L3   QUE L2 (S) (LUMINESC##### OR LUMINOS###)

=> s L3 (s) (fluoresc#### or fluoro#####)
          5   FILE ANABSTR
          4   FILE BIOENG
          1   FILE BIOSIS
         92   FILE BIOTECHABS
         92   FILE BIOTECHDS
  12 FILES SEARCHED...
          6   FILE BIOTECHNO
          1   FILE CABA
          4   FILE CAPLUS
          2   FILE CEABA-VTB
  21 FILES SEARCHED...
         16   FILE DGENE
  23 FILES SEARCHED...
          1   FILE DISSABS
          1   FILE DRUGU
          1   FILE EMBASE
          5   FILE ESBIOBASE
          2   FILE FROSTI
          1   FILE FSTA
  34 FILES SEARCHED...
         10   FILE GENBANK
         15   FILE IFIPAT
          4   FILE LIFESCI
          1   FILE MEDLINE
          1   FILE NTIS
          6   FILE PASCAL
  47 FILES SEARCHED...
          1   FILE PHIN
          2   FILE PROMT
```

```
          1   FILE SCISEARCH
         62   FILE USGENE
        408   FILE USPATFULL
         57   FILE USPAT2
  63 FILES SEARCHED...
         50   FILE WPIDS
          1   FILE WPIFV
         50   FILE WPINDEX

  31 FILES HAVE ONE OR MORE ANSWERS,   69 FILES SEARCHED IN STNINDEX

L4   QUE L3 (S) (FLUORESC#### OR FLUORO#####)

=> s L4 not py>2004
          0*  FILE ADISINSIGHT
          3   FILE ANABSTR
          2   FILE BIOENG
          1   FILE BIOSIS
         55   FILE BIOTECHABS
  11 FILES SEARCHED...
         55   FILE BIOTECHDS
          6   FILE BIOTECHNO
          2   FILE CAPLUS
          2   FILE CEABA-VTB
  17 FILES SEARCHED...
          0*  FILE CONFSCI
          6   FILE DGENE
  23 FILES SEARCHED...
          1   FILE DISSABS
          1   FILE EMBASE
          1   FILE ESBIOBASE
  31 FILES SEARCHED...
          0*  FILE FOREGE
          2   FILE FROSTI
          1   FILE FSTA
          5   FILE GENBANK
          7   FILE IFIPAT
          1   FILE LIFESCI
          1   FILE MEDLINE
          1   FILE NTIS
  46 FILES SEARCHED...
          5   FILE PASCAL
  48 FILES SEARCHED...
          0*  FILE PHAR
          1   FILE PHIN
          2   FILE PROMT
          0*  FILE PROUSDDR
          1   FILE SCISEARCH
         31   FILE USGENE
        148   FILE USPATFULL
         18   FILE USPAT2
  63 FILES SEARCHED...
          8   FILE WPIDS
          8   FILE WPINDEX

  28 FILES HAVE ONE OR MORE ANSWERS,   69 FILES SEARCHED IN STNINDEX

L5   QUE L4 NOT PY>2004

=> s L5 and lucifer###
          0*  FILE ADISINSIGHT
```

```
          6   FILE BIOTECHABS
          6   FILE BIOTECHDS
  12 FILES SEARCHED...
          2   FILE BIOTECHNO
          0*  FILE CONFSCI
  23 FILES SEARCHED...
          1   FILE ESBIOBASE
  31 FILES SEARCHED...
          0*  FILE FOREGE
          3   FILE GENBANK
          3   FILE IFIPAT
          1   FILE NTIS
  46 FILES SEARCHED...
          1   FILE PASCAL
  48 FILES SEARCHED...
          0*  FILE PHAR
          1   FILE PROMT
          0*  FILE PROUSDDR
         60   FILE USPATFULL
          5   FILE USPAT2
  63 FILES SEARCHED...

  11 FILES HAVE ONE OR MORE ANSWERS,   69 FILES SEARCHED IN STNINDEX

L6   QUE L5 AND LUCIFER###

=> d rank
F1          60   USPATFULL
F2           6   BIOTECHABS
F3           6   BIOTECHDS
F4           5   USPAT2
F5           3   GENBANK
F6           3   IFIPAT
F7           2   BIOTECHNO
F8           1   ESBIOBASE
F9           1   NTIS
F10          1   PASCAL
F11          1   PROMT


=> fil f1-f4, f6-f8
COST IN U.S. DOLLARS                        SINCE FILE      TOTAL
                                              ENTRY    SESSION
FULL ESTIMATED COST                           22.10      22.31

FILE 'USPATFULL' ENTERED AT 08:07:58 ON 18 MAR 2008
CA INDEXING COPYRIGHT (C) 2008 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'BIOTECHABS' ACCESS NOT AUTHORIZED

FILE 'BIOTECHDS' ENTERED AT 08:07:58 ON 18 MAR 2008
COPYRIGHT (C) 2008 THE THOMSON CORPORATION

FILE 'USPAT2' ENTERED AT 08:07:58 ON 18 MAR 2008
CA INDEXING COPYRIGHT (C) 2008 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'IFIPAT' ENTERED AT 08:07:58 ON 18 MAR 2008
COPYRIGHT (C) 2008 IFI CLAIMS(R) Patent Services (IFI)

FILE 'BIOTECHNO' ENTERED AT 08:07:58 ON 18 MAR 2008
COPYRIGHT (C) 2008 Elsevier Science B.V., Amsterdam. All rights reserved.
```

FILE 'ESBIOBASE' ENTERED AT 08:07:58 ON 18 MAR 2008

=> s L6
   5 FILES SEARCHED...
L7   77 L6

=> dup rem L7
PROCESSING COMPLETED FOR L7
L8   71 DUP REM L7 (6 DUPLICATES REMOVED)

=> d L8 ibib abs 1-35

L8   ANSWER 1 OF 71 USPATFULL on STN
ACCESSION NUMBER: 2004:334157 USPATFULL <<LOGINID::20080318>>
TITLE: Food allergens, method of detecting food allergens and
                        method of detecting food allergy-inducing foods
INVENTOR(S):   Morimatsu, Fumiki, Ibaraki, JAPAN
                        Takahata, Yoshihisa, Ibaraki, JAPAN
                        Matsumoto, Takashi, Ibaraki, JAPAN
                        Miyazawa, Izumi, Ibaraki, JAPAN
                        Shimizu, Muneshige, Ibaraki, JAPAN

                             NUMBER   KIND   DATE
                        ---------------- ------ --------
PATENT INFORMATION: US 2004265234   A1   20041230
APPLICATION INFO.:   US 2004-488461   A1   20040304 (10)
                        WO 2002-JP9066   20020905

                               NUMBER   DATE
                        ------------------ --------
PRIORITY INFORMATION: JP 2001-269592   20010905
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: BIRCH STEWART KOLASCH & BIRCH, PO BOX 747, FALLS
                        CHURCH, VA, 22040-0747
NUMBER OF CLAIMS: 5
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 837
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB   The present invention provides a method for detecting food allergens,
       antibodies and antigens to prepare the antibodies. The antigens of this
       invention are a mixture comprising multiple native and/or heated food
       allergens that IgE antibodies of food-allergy patients recognize. The
       antibodies of this invention are prepared by immunizing animals with the
       above-mentioned antigens. The food allergen-detecting method of this
       invention relates to the above-mentioned antibodies. As the method can
       detect food allergens and food allergy-inducing foods, it can provide
       safety to food allergy patients.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8   ANSWER 2 OF 71 USPATFULL on STN
ACCESSION NUMBER: 2004:291780 USPATFULL <<LOGINID::20080318>>
TITLE: Antibodies to a tumor-associated surface antigen for
                        delivery of diagnostic and therapeutic agents
INVENTOR(S):   Taylor, Ronald, Charlottesville, VA, UNITED STATES
                        Nardin, Alessandra, Paris, FRANCE
                        Sutherland, William M., Earlysville, VA, UNITED STATES

Sokoloff, Mitchell H., Hinsdale, IL, UNITED STATES
Chung, Leland, Lovingston, VA, UNITED STATES
PATENT ASSIGNEE(S): The University of Virginia Patent Foundation (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004228860	A1	20041118
APPLICATION INFO.:	US 2003-720019	A1	20031121 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1999-392500, filed on 9 Sep 1999, ABANDONED

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-99782P	19980910 (60)
	US 1999-123786P	19990311 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: JONES DAY, 222 EAST 41ST ST, NEW YORK, NY, 10017
NUMBER OF CLAIMS: 21
EXEMPLARY CLAIM: CLM-01-13
NUMBER OF DRAWINGS: 8 Drawing Page(s)
LINE COUNT: 2394
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to the treatment, inhibition and prevention of cancer by the administration of anti-C3b(i) antibodies. The invention also relates to the treatment, inhibition and prevention of cancer by the administration of IgM antibodies and/or complement components prior to the administration of anti-C3b(i) antibodies. The present invention further relates to the detection, imaging, diagnosis and monitoring of cancer utilizing C3b(i) specific antibodies.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 3 OF 71 USPATFULL on STN
ACCESSION NUMBER: 2004:267741 USPATFULL <<LOGINID::20080318>>
TITLE: Methods for producing polypeptide-tagged collections and capture systems containing the tagged polypeptides
INVENTOR(S): Ault-Riche, Dana, Los Gatos, CA, UNITED STATES
Atkinson, Bruce, Burlingame, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004209282	A1	20041021
APPLICATION INFO.:	US 2003-699088	A1	20031030 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-422923P	20021030 (60)
	US 2002-423018P	20021030 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: FISH & RICHARDSON, PC, 12390 EL CAMINO REAL, SAN DIEGO, CA, 92130-2081
NUMBER OF CLAIMS: 134
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 14 Drawing Page(s)
LINE COUNT: 13362
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Methods for evenly distributing tags on collections of molecules are provided. Also provided are assay methods that employ the tagged

collections.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 4 OF 71 USPATFULL on STN

ACCESSION NUMBER:	2004:253742 USPATFULL <<LOGINID::20080318>>
TITLE:	In vivo fluorescence sensors, systems, and related methods operating in conjunction with fluorescent analytes
INVENTOR(S):	Black, Robert D., Chapel Hill, NC, UNITED STATES Bolick, Natasha, Creedmoor, NC, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004197267	A1	20041007
APPLICATION INFO.:	US 2004-779907	A1	20040217 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2003-448349P	20030219 (60)
	US 2003-471706P	20030519 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	MYERS BIGEL SIBLEY & SAJOVEC, PO BOX 37428, RALEIGH, NC, 27627
NUMBER OF CLAIMS:	104
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	14 Drawing Page(s)
LINE COUNT:	2737

AB Methods, systems, devices and computer program product include: (i) administering a fluorescent analyte to a subject; (ii) repetitively emitting excitation light from an implanted sensor over a desired monitoring period; (iii) detecting fluorescence intensity in response to the excitation light using the implanted sensor that outputs the excitation light; and (iv) using data associated with the detected fluorescence intensity to perform at least one of: (a) calculate the concentration or dose of the analyte received proximate to the implanted sensor site; (b) evaluate the pharmacodynamic or pharmacokinetic activity of the fluorescent analyte; (c) confirm Ab attachment to a tumor site; (d) monitor a non-target site to confirm it is not unduly affected by a therapy; (e) monitor for changes in cellular properties; (f) use the calculated dose or concentration data to adjust or customize a therapeutic amount of the analyte administered to the subject; (g) confirm micelle concentration at a target site and then stimulate toxin release based on the confirmation; and (h) monitor for the expression of a protein produced from a gene therapy modification.

In particular embodiments, the intensity of the excitation signals emitted to the localized tissue can be varied in a predetermined manner to generate optical profiling data of the response of the tissue proximate the sensor.

L8 ANSWER 5 OF 71 USPATFULL on STN

ACCESSION NUMBER:	2004:184470 USPATFULL <<LOGINID::20080318>>
TITLE:	Compositions and methods for identifying plants having increased tolerance to imidazolinone herbicides
INVENTOR(S):	Cheung, Wing Y., Brossard, CANADA Gagnon, Marie-Josee, Montreal, CANADA Laforest, Martin, St-Luc, CANADA Landry, Benoit S., L'Acadie, CANADA

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004142353	A1	20040722
APPLICATION INFO.:	US 2003-695089	A1	20031028 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-421993P	20021029 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: BASF CORPORATION, 26 DAVIS DRIVE, RESEARCH TRIANGLE PARK, NC, 27709
NUMBER OF CLAIMS: 11
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 10 Drawing Page(s)
LINE COUNT: 915
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides compositions and methods for assaying commercially relevant imidazolinone herbicide tolerance conferred by a Brassica napus AHAS1 PM1 mutation and a Brassica napus AHAS3 PM2 mutation in a plant.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 6 OF 71 USPATFULL on STN
ACCESSION NUMBER: 2004:151406 USPATFULL <<LOGINID::20080318>>
TITLE: Compositions and methods for induction of proteins involved in xenobiotic metabolism
INVENTOR(S): Raucy, Judy, San Diego, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004115627	A1	20040617
APPLICATION INFO.:	US 2002-222679	A1	20020816 (10)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 2001-832621, filed on 11 Apr 2001, PENDING		

	NUMBER	DATE
PRIORITY INFORMATION:	WO 2001-US11819	20010411
	US 2000-196681P	20000412 (60)
	US 2000-241391P	20001017 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: DAVID R PRESTON & ASSOCIATES, 12625 HIGH BLUFF DRIVE, SUITE 205, SAN DIEGO, CA, 92130
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 24 Drawing Page(s)
LINE COUNT: 2424
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides improved cells and methods for identifying compounds that alter protein expression, such as xenobiotics, endobiotics, chemicals or drugs. The invention provides other benefits as well. One aspect of the present invention is a cell that includes a first nucleic acid molecule that includes: a promoter or enhancer operable for a nucleic acid molecule encoding a human or non-human protein involved in drug metabolism (such as an enzyme or transporter) and a reporter gene; and a second nucleic acid encoding a human or non-human intracellular receptor or transcription factor; so

that when the intracellular receptor or transcription factor is bound with a compound, the intracellular receptor, transporter or transcription factor can operably bind with the promoter or enhancer resulting in the expression of said reporter gene. Another aspect of the present invention is a method for evaluating compounds for the property of inducing the expression of a gene encoding a protein involved in drug metabolism, including; providing a test compound; contacting the test compound with a cell of the present invention; and detecting the expression of said reporter gene. This method can be a high throughput method.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 7 OF 71 USPATFULL on STN
ACCESSION NUMBER: 2004:126920 USPATFULL <<LOGINID::20080318>>
TITLE: Immunoassay method for membrane-bound matrix metalloprotease
INVENTOR(S): Aoki, Takanori, Takaoka, JAPAN
Yonezawa, Kayoko, Takaoka, JAPAN
Fujimoto, Noboru, Takaoka, JAPAN
Ogawa, Miwa, Takaoka, JAPAN
Iwata, Kazushi, Takaoka, JAPAN

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004096899	A1	20040520	
APPLICATION INFO.:	US 2003-432198	A1	20031027	(10)
	WO 2001-JP10136		20011120	

	NUMBER	DATE
PRIORITY INFORMATION:	JP 2000-352491	20001120

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Wenderoth Lind & Ponack, Suite 800, 2033 K Street NW, Washington, DC, 20006
NUMBER OF CLAIMS: 60
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 9 Drawing Page(s)
LINE COUNT: 3155
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB It is made possible to quantify MT1-MMP and to measure the enzymatic activity of MT1-MMP sensitively, accurately and quickly with simple operations and reagents. The MT1-MMP quantifications and the MT1-MMP enzymatic activity measurements can be carried out using quantitative immunoassays for MT1-MMP with anti-MT1-MMP Ab and reagents used therefor, further immunologically quantifying methods for a member selected from (i) MT1-MMP released and/or solubilized from cell membrane with a surfactant and/or a reducing agent and (ii) spontaneously solubilized MT1-MMP, reagents used therefor, solid-phased MT1-MMP, etc., thereby enabling the screening for a compound which promotes or inhibits the expression of MT1-MMP or a compound which promotes or inhibits the enzymatic activity of MT1-MMP, and facilitating the development and research for valuable pharmaceutical drugs. There are also provided a useful testing drug for cancer or cancer metastasis.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 8 OF 71 USPATFULL on STN
ACCESSION NUMBER: 2004:101218 USPATFULL <<LOGINID::20080318>>
TITLE: Compositions and methods for induction of proteins

involved in xenobiotic metabolism
INVENTOR(S): Raucy, Judy, San Diego, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004077080	A1	20040422
APPLICATION INFO.:	US 2003-642322	A1	20030815 (10)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2002-222679, filed on 16 Aug 2002, PENDING Continuation-in-part of Ser. No. US 2001-832621, filed on 11 Apr 2001, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-241391P	20001017 (60)
	US 2000-196681P	20000412 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: DAVID R PRESTON & ASSOCIATES, 12625 HIGH BLUFF DRIVE, SUITE 205, SAN DIEGO, CA, 92130
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 48 Drawing Page(s)
LINE COUNT: 3744
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides improved cells and methods for identifying compounds that alter protein expression, such as xenobiotics, endobiotics, chemicals or drugs. The invention provides other benefits as well. One aspect of the present invention is a cell that includes a first nucleic acid molecule that includes: a promoter or enhancer operable for a nucleic acid molecule encoding a human or non-human protein involved in drug metabolism (such as an enzyme or transporter) and a reporter gene; and a second nucleic acid encoding a human or non-human intracellular receptor or transcription factor; so that when the intracellular receptor or transcription factor is bound with a compound, the intracellular receptor, transporter or transcription factor can operably bind with the promoter or enhancer resulting in the expression of said reporter gene. Another aspect of the present invention is a method for evaluating compounds for the property of inducing the expression of a gene encoding a protein involved in drug metabolism, including; providing a test compound; contacting the test compound with a cell of the present invention; and detecting the expression of said reporter gene. This method can be a high throughput method.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 9 OF 71 USPATFULL on STN
ACCESSION NUMBER: 2004:70119 USPATFULL <<LOGINID::20080318>>
TITLE: Agent for detecting cancer's ability to metastasize
INVENTOR(S): Hirashima, Mitsuomi, Kagawa, JAPAN
Yamauchi, Akira, Kagawa, JAPAN
Kageshita, Toshiro, Kumamoto, JAPAN
Nakamura, Takanori, Kagawa, JAPAN
Nishi, Nozomu, Kagawa, JAPAN

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004053346	A1	20040318
APPLICATION INFO.:	US 2003-415586	A1	20030905 (10)
	WO 2001-JP9561		20011031

	NUMBER	DATE
PRIORITY INFORMATION:	JP 2000-335077	20001101

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: WENDEROTH, LIND & PONACK, L.L.P., 2033 K STREET N. W., SUITE 800, WASHINGTON, DC, 20006-1021
NUMBER OF CLAIMS: 22
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 7 Drawing Page(s)
LINE COUNT: 2298
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB By disclosing part of metastasis mechanisms in cancer cells, the metastatic potential of cancer cells will be determinable. Anti-galectin-9 Ab against galectin-9 is contained as an effective component with or without others, thereby enabling the evaluation or detection of galectin-9 expression levels in cancer cells wherein the metastatic potential of the cancer cells can be assessed or detected.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 10 OF 71 USPATFULL on STN
ACCESSION NUMBER: 2004:70118 USPATFULL <<LOGINID::20080318>>
TITLE: Marker for probing the therapeutic efficacy of drugs
INVENTOR(S): Yamauchi, Akira, Kagawa, JAPAN
Murao, Koji, Kagawa, JAPAN
Nishi, Nozomu, Kagawa, JAPAN
Hirashima, Mitsuomi, Kagawa, JAPAN

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004053345	A1	20040318	
APPLICATION INFO.:	US 2003-383073	A1	20030307	(10)

	NUMBER	DATE
PRIORITY INFORMATION:	JP 2002-263093	20020909

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: WENDEROTH, LIND & PONACK, L.L.P., 2033 K STREET N. W., SUITE 800, WASHINGTON, DC, 20006-1021
NUMBER OF CLAIMS: 3
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Page(s)
LINE COUNT: 1666
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Although adjuvant, or additional, therapy after surgery (e.g., adjuvant, or additional, hormonal therapy after breast cancer surgery) is performed to prevent postoperative recurrence of malignant tumors such as breast cancer, the incidence of disease recurrence still remains even if a representative drug, tamoxifen, commonly used is given. Thus, if it is possible to predict whether malignant tumors are reliably curable with tamoxifen or whether therapeutic drugs other than tamoxifen should be selected or not against such malignant tumors, it will greatly assist in the therapeutic guideline for preventing postoperative recurrence. There is a possibility that menin regulates the ER transcription activity in breast cancer cells. The expression of menin is remarkably responsible for the efficacy of estrogen antagonists (e.g., tamoxifen) having an inhibitory activity on estrogen binding to the ER. Techniques utilizing the present findings are provided. That is, provided is use of menin and menin expression gene as markers for probing the efficacy of

therapeutic drugs (e.g., anti-cancer agents, antineoplastic agents) on tumor cells (e.g., breast cancer) or drug resistance markers for such therapeutic drugs, related reagents and methods for measurement/detection as well as systems utilizing them.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 11 OF 71 USPATFULL on STN

ACCESSION NUMBER:	2004:31126 USPATFULL <<LOGINID::20080318>>			
TITLE:	Method for determining the peptide hormone activities or the steroid hormone activities of a material or substance mixture			
INVENTOR(S):	Allera, Axel, Lohmar, GERMANY, FEDERAL REPUBLIC OF Wildt, Ludwig, Herzogenaurach, GERMANY, FEDERAL REPUBLIC OF			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004023264	A1	20040205	
APPLICATION INFO.:	US 2003-380963	A1	20030616	(10)
	WO 2001-DE3628		20010920	
	NUMBER		DATE	
PRIORITY INFORMATION:	DE 2000-10046647		20000920	
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	APPLICATION			
LEGAL REPRESENTATIVE:	FRISHAUF, HOLTZ, GOODMAN & CHICK, PC, 767 THIRD AVENUE, 25TH FLOOR, NEW YORK, NY, 10017-2023			
NUMBER OF CLAIMS:	10			
EXEMPLARY CLAIM:	1			
NUMBER OF DRAWINGS:	15 Drawing Page(s)			
LINE COUNT:	781			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention relates to a method for determining the peptide hormone activities or the steroid hormone activities of a material or substance mixture involving the following steps: (a) presenting at least one starting cell with or without endogenous peptide hormone receptors or steroid hormone receptors; (b) transfecting the cell with a specific recombinant reporter gene construct, which has the ability to express a product that is induced and can be measured by the hormone activity of the material; (c) introducing a material to be examined into the transfected cell; (d) producing an easily determinable signal-generating reporter gene translation product through the transfected cell by using the inductive effect of the material on the hormone-reactive promoter situated before the reported gene; (e) measuring the reporter gene translation product of the transfected cell, and; (f) determining the hormone activity of the material from the measured result.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 12 OF 71 USPATFULL on STN

ACCESSION NUMBER:	2004:24676 USPATFULL <<LOGINID::20080318>>
TITLE:	Compositions selective for adenosine diphosphate and methods of using same
INVENTOR(S):	Diener, John L., Cambridge, MA, UNITED STATES Srinivasan, Jayaram, Murrysville, PA, UNITED STATES Hamaguchi, Nobuko, Framingham, MA, UNITED STATES Blanchard, Jill, Arlington, MA, UNITED STATES Kurz, Jeffrey, Somerville, MA, UNITED STATES Kurz, Markus, Newton, MA, UNITED STATES

Cload, Sharon T., Cambridge, MA, UNITED STATES
Epstein, David, Belmont, MA, UNITED STATES
Wilson, Charles, Concord, MA, UNITED STATES
Stanton, Martin, Stow, MA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004018515	A1	20040129
APPLICATION INFO.:	US 2003-406027	A1	20030402 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-369680P	20020403 (60)
	US 2002-370196P	20020405 (60)
	US 2003-437949P	20030103 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MINTZ, LEVIN, COHN, FERRIS, GLOVSKY, AND POPEO, P.C., ONE FINANCIAL CENTER, BOSTON, MA, 02111
NUMBER OF CLAIMS: 100
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 80 Drawing Page(s)
LINE COUNT: 5765
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Compositions which recognize and report on the concentration selectively adenosine diphosphate (ADP) and methods of making and using them are provided. The invention further relates to methods of using the compositions to monitor function of biological agents. Reagents and systems for performing the methods are also provided. The methods of the invention are useful in diagnostic applications and drug optimization.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 13 OF 71 USPATFULL on STN
ACCESSION NUMBER: 2004:18781 USPATFULL <<LOGINID::20080318>>
TITLE: Detection of heteroduplex polynucleotides using mutant nucleic acid repair enzymes with attenuated catalytic activity
INVENTOR(S): Yuan, Chong-Sheng, San Diego, CA, UNITED STATES
Datta, Abhijit, Carlsbad, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004014083	A1	20040122
APPLICATION INFO.:	US 2003-373238	A1	20030224 (10)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2000-514016, filed on 25 Feb 2000, PENDING
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Peng Chen, Morrison & Foerster LLP, Suite 500, 3811 Valley Centre Drive, San Diego, CA, 92130-2332
NUMBER OF CLAIMS: 105
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 10442
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Methods for detecting, localizing and removing abnormal base-pairing in a nucleic acid duplex are provided. These methods can be used for prognosis and diagnosis of diseases, disorders, pathogenic infections and nucleic acid polymorphisms. Combinations, kits and articles of manufacture for use in these methods are also provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 14 OF 71 BIOTECHDS COPYRIGHT 2008 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2004-25307 BIOTECHDS <<LOGINID::20080318>>
TITLE: Detecting target nucleic acids, e.g. viral nucleic acid, comprises subjecting the sample DNA and primer to a polymerase reaction and detecting released pyrophosphate enzymatically;
virus DNA detection using polymerase chain reaction
AUTHOR: HONG Y
PATENT ASSIGNEE: TEMASEK LIFE SCI LAB
PATENT INFO: WO 2004090167 21 Oct 2004
APPLICATION INFO: WO 2004-SG93 14 Apr 2004
PRIORITY INFO: US 2003-462308 14 Apr 2003; US 2003-462308 14 Apr 2003
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2004-766422 [75]
AN 2004-25307 BIOTECHDS <<LOGINID::20080318>>
AB DERWENT ABSTRACT:

NOVELTY - Identifying the presence of a target nucleic acid in a sample comprises subjecting the sample DNA and primer to a polymerase reaction and detecting any release of pyrophosphate (PPi) enzymatically.

DETAILED DESCRIPTION - Identifying the presence of a target nucleic acid in a sample, where the target nucleic acid is replicated and the replication of the target is detected as the consumption of a deoxynucleotide triphosphate precursor, comprises: (a) adding an oligonucleotide primer which hybridizes to the sample target nucleic acid to the sample; (b) subjecting the sample DNA and primer to a polymerase reaction in the presence of a mixture of all dNTP's required for replication of the target nucleic acid, where the deoxynucleotides will become incorporated and release PPi proportional to the length of the DNA extension product; and (c) detecting any release of PPi enzymatically, where any release of PPi is indicative of incorporation of deoxynucleotide or dideoxynucleotide and the presence of the target DNA. An INDEPENDENT CLAIM is also included for a kit, used in performing the method above, comprising a polymerase, detection enzyme means for identifying PPi release, dNTP's, or optionally deoxynucleotide analogues, optionally including in place of dATP, a dATP analogue which is capable of acting as a substrate for a polymerase but incapable of acting as a substrate for the PPi-detection enzyme, and optionally a target specific primer which hybridizes to the target DNA and is recognized as a primer by a polymerase, where the polymerase replicates the target DNA.

BIOTECHNOLOGY - Preferred Method: The target nucleic acid is replicated in a reaction, e.g. polymerase extension reaction, ligase chain reaction (LCR), rolling circle replication reaction (RCR), or nucleic acid sequence based amplification reaction (MASBA), preferably PCR. The release of PPi is detected by means of a Luciferase-Luciferin-based reaction. PPi release is detected using ATP sulfurylase and luciferase. The PPi detection enzymes are included in the polymerase reaction step and the polymerase reaction and PPi release detection steps are performed substantially simultaneously. The method further comprises adding a dATP analogue, which is capable of acting as a substrate for a polymerase, but incapable of acting as a substrate for a PPi detection enzyme. The sample DNA or oligonucleotide primer is immobilized or provided with means for attachment to a solid support. An exonuclease deficient high fidelity polymerase or a heat resistant polymerase is

used. The sample DNA is first amplified. The method is used with a multiplicity of sample DNA sequences, where the DNA sequences are arranged in assay format on a solid surface. The nucleic acid sample is obtained from a biological sample. The target nucleic acid is a microbial nucleic acid, preferably a viral nucleic acid. The nucleic acid sample is obtained from a food source i.e. a plant. The target nucleic acid contains a nucleic acid sequence non-native to the sample.

USE - The method and kit are useful for detecting and/or quantifying target nucleic acid, e.g. microbial nucleic acid, preferably a viral nucleic acid, in a sample.

EXAMPLE - Samples of maize containing the transgenic GMO corn line MON810 were obtained. Genomic DNA was isolated from the maize sample. Specific primers were used to amplify a 19 bp fragment of the transgene. PCR was performed. Autofluorescence was carried out by pyro luminescence, which detects the release of pyrophosphate (PPi) from nucleotide triphosphates by means of a Luciferase-Luciferin-based reaction. A 5 microl sample of the PCR product was mixed with fresh autofluorescence detection buffer immediately before fluorescence readings were taken. A 149 bp DNA fragment was detectable on the agarose gel for the positive control after 10 cycles of PCR at an autofluorescence level much higher than the negative controls having no template DNA. Results demonstrated that detection of pyrophosphate levels by Luciferin autofluorescence following a PCR reaction can be used to detect the presence of the transgenes of GMOs.(34 pages)

L8 ANSWER 15 OF 71 BIOTECHDS COPYRIGHT 2008 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2004-21643 BIOTECHDS <<LOGINID::20080318>>
TITLE: New biosensor comprising luminescent or fluorescent filamentous fungi, useful for detecting component substances within a sample or in studying the mode of action of fungicides and toxic molecules;
for use as a fungicide
AUTHOR: HICKEY P C
PATENT ASSIGNEE: LUX BIOTECHNOLOGY LTD
PATENT INFO: WO 2004076685 10 Sep 2004
APPLICATION INFO: WO 2004-GB839 1 Mar 2004
PRIORITY INFO: GB 2004-183 7 Jan 2004; GB 2003-4625 28 Feb 2003
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2004-662020 [64]
AN 2004-21643 BIOTECHDS <<LOGINID::20080318>>
AB DERWENT ABSTRACT:

NOVELTY - A biosensor comprising luminescent or fluorescent filamentous fungi where the light output varies in response to the presence or absence of a predetermined test substance, is new.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for an assay to determine the presence of a predetermined test substance in a sample.

BIOTECHNOLOGY - Preferred Biosensor: The filamentous fungi produces a luciferase, e.g. a Gaussia luciferase or a Pleuromamma luciferase. The fungus is Aspergillus sp., Neurospora sp., Magnaporthe grisea or Sclerotinia sclerotiorum. The luminescence or fluorescence of the fungi is ATP independent. Expression of a gene encoding a luminescent or fluorescent protein in the fungus is driven by an inducible promoter or enhancer. The fungus is genetically engineered to comprise a constitutive or inducible promoter or enhancer genetically linked to the gene encoding the luminescent or fluorescent protein.

The luminescence or fluorescence of the filamentous fungi is increased or decreased in the presence of the test substance. The filamentous fungi are in the form of an array. The biosensor includes an indicator to show the viability of the fungus. Preferred Method: Determining the presence of a predetermined test substance in a sample comprises exposing the sample to a filamentous fungus having an ability to luminesce or fluoresce where the luminescent or fluorescent output will vary depending upon presence or absence of the test substance, and measuring the luminescent or fluorescent output from the fungi, and determining the presence of the test substance in the sample. The assay further includes positive and negative controls. Spores of the fungus are immobilized in an array. The fungus is in the form of a fibrous mat. The light output is measured by a CCD camera, photodiode, photomultiplier or luminometer.

USE - The biosensor and methods are useful for detecting component substances within a sample, in studying the mode of action of fungicides and toxic molecules, or in identifying compounds affecting the expression of gene involved in diseases.

EXAMPLE - Wild type and cot-2 protoplasts were made from conidia (spores). Neurospora protoplasts were produced and transformed according to a method adapted from Vollmer and Yanofsky (1986). Transformed protoplasts were selected and homokaryons purified by growth, for three generations on hygromycin-amended media (150microg hygromycin/ml media). Cot-2 is a-colonial temperature sensitive mutant of Neurospora crassa. Cot-2 grows normally and is almost-indistinguishable from wild type at 25degreesC, but is temperature sensitive at 34degreesC and above, resulting in cessation of radial growth of the colony, hyperbranched phenotype and produces smaller dense colonies. This phenotype is useful due to the ability to halt growth. Growth resumes as normal when the temperature is shifted back to 25degreesC. Conidia produced as described in 'Fungal Strains and Culture Conditions', were harvested in 50-ml liquid Vogel's media and the resulting solution was passed through a funnel containing a cheesecloth filter into a 1L flask and incubated at 4degreesC overnight for rehydration. Germination of the conidia was initiated by incubating at 24degreesC on a shaker (120 rpm). Once a large proportion of the conidial population had produced-germ tubes 1 to 4 conidial diameters in length, the solution was decanted into sterile SO ml tubes and centrifuged at room temperature at 1400 rpm for 8 minutes. For each tube, the supernatant was removed, the pellet resuspended in 30 ml sterile distilled water, and the centrifugation repeated. This wash was performed twice more. After the final wash conidia from all the tubes were combined, resuspended in 1 mg NovozymeT 234 Cell Wall Lysing Enzyme in 2 ml I M sorbitol per 2x10 to the power pf 9 conidia (filter sterilised) and incubated horizontally on a shaker at 55 rpm, 31degreesC. Once protoplasts had formed (i.e. spherical cells that burst upon addition of dH20 are visible when the solution is examined under the microscope) the solution was centrifuged for 10 minutes at 800 rpm at 4degreesC. The supernatant was removed and the protoplasts washed twice by re-suspending in 10 ml chilled 1 M sorbitol and repeating the centrifugation. The pellet was then resuspended in 10 ml chilled STC (i.e. STC on ice,) and the number of protoplasts per ml estimated using a haemocytometer. The solution was centrifuged once more and the pellet-resuspended in a volume of storage solution that gave a final concentration of approximately 107 protoplasts per ml. Protoplasts were divided into 400microl aliquots and stored at -80degreesC. For each transformation, 20 microg of heparin (5 mg ml) plus 3microg of DNA were added to 100microg of protoplasts and incubated on ice for 30 minutes. 1 ml of PTC was added to the reaction mixture, which was then incubated at room temperature for 20 minutes. The reaction mixture was mixed with 8 to 10 ml RM, poured into a Petri dish containing 15 to 20 ml hygromycin

(150microg hygromycin/ml) amended PM and incubated at 34degreesC or 24degreesC for 5 to 10 days. (54 pages)

L8 ANSWER 16 OF 71 IFIPAT COPYRIGHT 2008 IFI on STN

AN 10663863 IFIPAT;IFIUDB;IFICDB <<LOGINID::20080318>>

TITLE: LUMINESCENCE-BASED METHODS AND PROBES FOR MEASURING CYTOCHROME P450 ACTIVITY

INVENTOR(S): Cali; James J., Verona, WI, US
Daily; William, Santa Maria, CA, US
Frackman; Susan, Madison, WI, US
Hawkins; Erika, Madison, WI, US
Ho; Samuel Kin Sang, New Bedford, MA, US
Klaubert; Dieter, Arroyo Grande, CA, US
Wood; Keith V., Mount Horeb, WI, US

PATENT ASSIGNEE(S): Promega Corporation, US

AGENT: MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP, 300 S. WACKER DRIVE, 32ND FLOOR, CHICAGO, IL, 60606, US

	NUMBER	PK	DATE
PATENT INFORMATION:	US 2004171099	A1	20040902
APPLICATION INFORMATION:	US 2003-665314		20030919

	NUMBER	DATE
PRIORITY APPLN. INFO.:	US 2002-412254P	20020920 (Provisional)
	US 2003-483309P	20030627 (Provisional)
FAMILY INFORMATION:	US 2004171099	20040902

DOCUMENT TYPE: Utility
Patent Application - First Publication

FILE SEGMENT: CHEMICAL
APPLICATION

ENTRY DATE: Entered STN: 3 Sep 2004
Last Updated on STN: 25 Sep 2006

NUMBER OF CLAIMS: 168 17 Figure(s).
DESCRIPTION OF FIGURES:

FIG. 1. Luminescent CYP450 reaction scheme.

FIG. 2. Structures: D-luciferin ((4S)-4,5-dihydro-2-(6-hydroxybenzothiazolyl)-4-thiazolecarboxylic acid) and D-luciferin derivatives.

FIG. 3. Two-step luminescent CYP450 reactions. D-luciferin derivatives were incubated in a CYP450 reaction mix for 60 minutes at 37 degrees C. before combining with a luciferase reaction mixture. In-CYP450 controls, CYP450 Sf9 cell microsomes were replaced with control (no CYP450) Sf9 cell membranes (panels B, C, D and E) or H2O (panel A) or both (panel F, G, H, and I). Luminescence was read within 12 minutes of combining the reactions on a Turner Reporter (panels A, B, C and E) or Berthold Orion (panels D, F, G, and H) luminometer.

FIG. 4. Time-dependence of CYP450/substrate incubation in twostep ***luminescent*** CYP450 reactions. D-luciferin derivatives were incubated in a CYP450 reaction mix for the indicated times at 37 degrees C. before combining with a luciferase reaction mixture. For-CYP450 controls CYP450 Sf9 cell microsomes were replaced with H2O. ***Luminescence*** was read within 12 minutes of combining the reactions on a Turner Reporter (panels A and C) or Berthold Orion (panel B) luminometer.

FIG. 5. Time course of light output from two-step luminescent CYP450 reactions. Luc ME was incubated in CYP450 reaction mixes for 60 minutes at 37 degrees C. before combining with a luciferase reaction mixture. In CYP450 controls CYP450 Sf9 cell microsomes were replaced with H2O. ***Luminescence*** was read on a Turner Reporter luminometer beginning 3

minutes after combining the reactions and at successive intervals as indicated for 284 minutes.

FIG. 6. One-step luminescent CYP450 assays at room temperature. Luc ME was incubated in combined CYP450 and ***luciferase*** reaction mixes at room temperature (22 degrees C.). For-CYP450 controls CYP450 Sf9 cell microsomes were replaced with H2O. CYP450 and a luciferase reaction mix were added simultaneously to a CYP450 reaction mix and light output was read immediately (time=0). Readings were then taken every 4.25 minutes for 15.5 hours on a Turner Reporter luminometer.

FIG. 7. One-step luminescent CYP450 assays at 37 degrees C. Dluciferin derivatives were incubated in combined CYP450 and ***luciferase*** reaction mixes at 37 degrees C. For-CYP450 controls CYP450 Sf9 cell microsomes were replaced with H2O. CYP450 and a luciferase reaction mix were added simultaneously to a CYP450 reaction mix and light output was read immediately (time=0). Readings were then taken every 10 minutes for 3 hours on a Turner 20/20 luminometer.

FIG. 8. Pooled human liver microsomes in two-step luminescent CYP450 reactions. D-luciferin derivatives were incubated in a CYP450 reaction mix with pooled human liver microsomes for 60 minutes at 37 degrees C. before combining with a luciferase reaction mixture. For controls liver microsomes were replaced with control (no CYP450) Sf9 cell membranes. ***Luminescence*** was read within 12 minutes of combining the reactions on a Berthold Orion luminometer. Vehicle for sulfaphenazole, ketoconazole and alpha-naphthoflavone was 1% acetonitrile and 1 mg/mL bovine serum albumin in H2O. Values labeled "nt" are vehicle controls. Concentrations of sulfaphenazole, ketoconazole and alphanaphthoflavone in the reactions were 100 micromolar, 100 micromolar and 10 micromolar, respectively.

FIG. 9. Two-step detection of CYP450 de-picolinylase activity. Dluciferin derivatives luc2PE, luc3PE, and luc4PE were incubated in a CYP450 reaction mix for 60 minutes at 37 degrees C. before combining with a ***luciferase*** reaction mixture. In this Figure, the bars labeled "Sf9" are the controls. These are Sf9 cell membranes without CYP450 expression. ***Luminescence*** was read within 12 minutes of combining the reactions on a Berthold Orion luminometer.

FIG. 10. CYP450-catalyzed conversion of luciferin derivatives to ***luciferin.*** Luciferin derivatives (100 micromolar) were incubated in a CYP450 reaction mix for the indicated time intervals. At the end of each time interval, the reaction mixture was quenched with Tergitol to 0.1% (v/v), then frozen in liquid nitrogen. 95 microliter aliquots of the reaction mixture were analyzed by HPLC and luciferin was detected by ***fluorescence*** with excitation at 330 nm and emission at 520 nm. The zero time points represent the luciferin content of the derivatives from controls (no enzyme).

FIG. 11. Detection of CYP450 inhibition by known CYP450 substrates. ***Luciferin*** derivatives as substrates for luminescent CYP450 ***assays*** were evaluated as probes for detecting other CYP450 substrates. CYP450 substrates tested were diclofenac for CYP2C9 and phenacetin for CYP1A1 and CYP1A2. The reactions were performed as described in Example 1 except the first step (CYP450 reaction) was in a 50 microliter reaction volume with 1 picomole of CYP450. In the second step a 50 microliter ***luciferase*** reaction was added to give final concentrations of 50 micrograms/mL Ultra Glo luciferase, 200 micromolar ATP, 0.1% Tergitol (v/v), 4.0 mM MgSO4 and 100 mM Tricine pH 8.4. Panel A illustrates inhibition of CYP1A2 by phenacetin using Luc ME as substrate. Panel B illustrates inhibition of CYP1A1 by phenacetin using Luc CEE as substrate. Panel C illustrates inhibition of CYP2C9 by diclofenac using HLuc as substrate.

FIG. 12: P450 action on methoxy-coelenterazine HH, coelenterazine HH and coelenterazine by chemiluminescent and bioluminescent detection. Panel A shows bioluminescence from methoxy-coelenterazine-HH in relative light units (RLU) generated in a Renilla luciferase containing reaction

following incubation of methoxy-coelenterazine HH with (+) or without (-) various P450 isozymes. Panel B shows the fold increase in bioluminescence from reactions containing methoxycoelenterazine HH and P450 (+P450 RLU/-P450 RLU). Panel C shows chemiluminescence from methoxy-coelenterazine HH in RLU generated following incubation of methoxy-coelenterazine HH with (+) or without (-) various P450 isozymes. Panel D shows the fold increase in chemiluminescence from reactions containing methoxy-coelenterazine HH and P450 (+P450 RLU/-P450 RLU). Panel E shows bioluminescence from coelenterazine HH in RLU generated in a Renilla luciferase containing reaction following incubation of coelenterazine HH with (+) or without () various P450 isozymes. Panel F shows the fold decrease in bioluminescence from reactions containing coelenterazine HH and P450 (+P450 RLU/-P450 RLU). Panel G shows chemiluminescence from coelenterazine HH in RLU generated following incubation of coelenterazine HH with (+) or without (-) various P450 isozymes. Panel H shows the decrease in chemiluminescence from reactions containing coelenterazine HH and P450 (+P450 RLU/-P450 RLU). Panel I shows bioluminescence from coelenterazine in RLU generated in a Renilla luciferase containing reaction following incubation of coelenterazine with (+) or without (-) various P450 isozymes. Panel J shows the decrease in bioluminescence from reactions containing coelenterazine and P450 (+P450 RLU/P450 RLU). Panel K shows chemiluminescence from coelenterazine in RLU generated following incubation of coelenterazine with (+) or without (-) various P450 isozymes. Panel L shows the decrease in chemiluminescence from reactions containing coelenterazine and P450 (+P450 RLU/-P450 RLU).

FIG. 13. Protection of luciferase from inhibitory buffer using yeast iPPase. Yeast inorganic pyrophosphatase was found to be effective in reversing iPP inhibition of luciferase when inhibitory KPO4 buffer used.

FIG. 14. Inorganic pyrophosphatases protect luciferase from pyrophosphatase contamination. Inorganic pyrophosphatases from different sources were found to reverse iPP inhibition of luciferase when inhibitory KPO4 buffer is used.

FIG. 15. Protection of luciferase from added iPP using iPPase. Inorganic pyrophosphatase was found to be effective in reversing iPP inhibition of a luciferase-based reaction when iPP is added to the reaction.

FIG. 16. Cell-based Luminescent CYP450 Assays. Primary rat hepatocytes were treated for 2 days with inducers of CYP450 gene expression: 5 micromolar 3-methylcholanthrene (MC), 50 micromolar dexamthasone (Dex) or 50 micromolar rifampicin (Rif) and their vehicle controls, 0.05, 0.1 and 0.1% DMSO, respectively (uninduced); and an inhibitor of CYP450: 100 micromolar troleandomycin (Tro). The induction medium was then replaced with 300 microliters of 100 micromolar luciferin-CEE (panels A and B), 200 micromolar luciferin-BE or 200 micromolar luciferin-BE plus Tro dissolved in hepatocyte culture medium and allowed to incubate for 4 hours. 100 microliters of medium was then removed from wells and combined with luciferin detection reagent (see example 15) and 200 microliters of luciferin detection reagent was added to the remaining 200 microliters of medium on cells. Luminescence from 200 microliters of culture medium reactions (panels A & C) and cell lysate reactions (panels B & D) was quantified.

FIG. 17. Stabilization of luminescent signals using ***luciferase*** inhibitors. Inhibition of luciferase by an inhibitor 2-(4aminophenyl)-6-methylbenzothiazole (APMBT) or 2-amino-6-methyl benzothiazole (AMBT) stabilizes the luminescent signal in a ***luminescent*** CYP450 assay. 50 microliter CYP1A1 reactions (0.5 pmol recombinant CYP1A1 enzyme, 30 mu M Luciferin chloroethyl ether, 100 mM KPO4, 1.3 mM NADP+, 3.3 mM glucose-6-phosphate, 3. 3 mM MgCl2, 0.02 unit glucose-6-phosphate dehydrogenase) were incubated at 37 degrees C. for 20 min. After the incubation, 50 microliters of a ***luciferin*** detection reagent (100 micrograms/mL thermostable ***luciferase*** (from Photuris pennsylvanica), 400 micromolar ATP, 0.6% Prionex, 2 units/mL iPPase, 200 mM Tricine pH 8.4, 20 mM MgSO4, 2% Tergitol)

containing either 100 micromolar APMBT, 100 micromolar AMBT, or no inhibitor were added to each aliquot of CYP1A1 reaction. Luminescence was read immediately and at subsequent 5 minute intervals for 1 hour.

AB The present invention provides methods, compositions, substrates, and kits useful for analyzing the metabolic activity in cells, tissue, and animals and for screening test compounds for their effect on cytochrome P450 activity. In particular, a one-step and two-step methods using luminogenic molecules, e.g. luciferin or coelenterazines, that are cytochrome P450 substrates and that are also bioluminescent enzyme, e.g., luciferase, pro-substrates are provided. Upon addition of the luciferin derivative or other luminogenic molecule into a P450 reaction, the P450 enzyme metabolizes the molecule into a bioluminescent enzyme substrate, e.g., luciferin and/or luciferin derivative metabolite, in a P450 reaction. The resulting metabolite(s) serves as a substrate of the bioluminescent enzyme, e.g., luciferase, in a second lightgenerating reaction. Luminescent cytochrome P450 assays with low background signals and high sensitivity are disclosed and isoform selectivity is demonstrated. The present invention also provides an improved method for performing luciferase reactions which employs added pyrophosphatase to remove inorganic pyrophosphate, a luciferase inhibitor which may be present in the reaction mixture as a contaminant or may be generated during the reaction. The present method further provides a method for stabilizing and prolonging the luminescent signal in a luciferase-based assay using luciferase stabilizing agents such as reversible luciferase inhibitors.

CLMN 168 17 Figure(s).

FIG. 1. Luminescent CYP450 reaction scheme.

FIG. 2. Structures: D-luciferin ((4S)-4,5-dihydro-2-(6-hydroxybenzothiazolyl)-4-thiazolecarboxylic acid) and D-luciferin derivatives.

FIG. 3. Two-step luminescent CYP450 reactions. D-luciferin derivatives were incubated in a CYP450 reaction mix for 60 minutes at 37 degrees C. before combining with a luciferase reaction mixture. In-CYP450 controls, CYP450 Sf9 cell microsomes were replaced with control (no CYP450) Sf9 cell membranes (panels B, C, D and E) or H2O (panel A) or both (panel F, G, H, and I). Luminescence was read within 12 minutes of combining the reactions on a Turner Reporter (panels A, B, C and E) or Berthold Orion (panels D, F, G, and H) luminometer.

FIG. 4. Time-dependence of CYP450/substrate incubation in twostep luminescent CYP450 reactions. D-luciferin derivatives were incubated in a CYP450 reaction mix for the indicated times at 37 degrees C. before combining with a luciferase reaction mixture. For-CYP450 controls CYP450 Sf9 cell microsomes were replaced with H2O. Luminescence was read within 12 minutes of combining the reactions on a Turner Reporter (panels A and C) or Berthold Orion (panel B) luminometer.

FIG. 5. Time course of light output from two-step luminescent CYP450 reactions. Luc ME was incubated in CYP450 reaction mixes for 60 minutes at 37 degrees C. before combining with a luciferase reaction mixture. In CYP450 controls CYP450 Sf9 cell microsomes were replaced with H2O. Luminescence was read on a Turner Reporter luminometer beginning 3 minutes after combining the reactions and at successive intervals as indicated for 284 minutes.

FIG. 6. One-step luminescent CYP450 assays at room temperature. Luc ME was incubated in combined CYP450 and luciferase reaction mixes at room temperature (22 degrees C.). For-CYP450 controls CYP450 Sf9 cell microsomes were replaced with H2O. CYP450 and a luciferase reaction mix were added simultaneously to a CYP450 reaction mix and light output was read

immediately (time=0). Readings were then taken every 4.25 minutes for 15.5 hours on a Turner Reporter luminometer.

FIG. 7. One-step luminescent CYP450 assays at 37 degrees C. Dluciferin derivatives were incubated in combined CYP450 and luciferase reaction mixes at 37 degrees C. For-CYP450 controls CYP450 Sf9 cell microsomes were replaced with H2O. CYP450 and a luciferase reaction mix were added simultaneously to a CYP450 reaction mix and light output was read immediately (time=0). Readings were then taken every 10 minutes for 3 hours on a Turner 20/20 luminometer.

FIG. 8. Pooled human liver microsomes in two-step luminescent CYP450 reactions. D-luciferin derivatives were incubated in a CYP450 reaction mix with pooled human liver microsomes for 60 minutes at 37 degrees C. before combining with a luciferase reaction mixture. For controls liver microsomes were replaced with control (no CYP450) Sf9 cell membranes. Luminescence was read within 12 minutes of combining the reactions on a Berthold Orion luminometer. Vehicle for sulfaphenazole, ketoconazole and alpha-naphthoflavone was 1% acetonitrile and 1 mg/mL bovine serum albumin in H2O. Values labeled "nt" are vehicle controls. Concentrations of sulfaphenazole, ketoconazole and alphanaphthoflavone in the reactions were 100 micromolar, 100 micromolar and 10 micromolar, respectively.

FIG. 9. Two-step detection of CYP450 de-picolinylase activity. Dluciferin derivatives luc2PE, luc3PE, and luc4PE were incubated in a CYP450 reaction mix for 60 minutes at 37 degrees C. before combining with a luciferase reaction mixture. In this Figure, the bars labeled "Sf9" are the controls. These are Sf9 cell membranes without CYP450 expression. Luminescence was read within 12 minutes of combining the reactions on a Berthold Orion luminometer.

FIG. 10. CYP450-catalyzed conversion of luciferin derivatives to luciferin. Luciferin derivatives (100 micromolar) were incubated in a CYP450 reaction mix for the indicated time intervals. At the end of each time interval, the reaction mixture was quenched with Tergitol to 0.1% (v/v), then frozen in liquid nitrogen. 95 microliter aliquots of the reaction mixture were analyzed by HPLC and luciferin was detected by fluorescence with excitation at 330 nm and emission at 520 nm. The zero time points represent the luciferin content of the derivatives from controls (no enzyme).

FIG. 11. Detection of CYP450 inhibition by known CYP450 substrates. Luciferin derivatives as substrates for luminescent CYP450 assays were evaluated as probes for detecting other CYP450 substrates. CYP450 substrates tested were diclofenac for CYP2C9 and phenacetin for CYP1A1 and CYP1A2. The reactions were performed as described in Example 1 except the first step (CYP450 reaction) was in a 50 microliter reaction volume with 1 picomole of CYP450. In the second step a 50 microliter luciferase reaction was added to give final concentrations of 50 micrograms/mL Ultra Glo luciferase, 200 micromolar ATP, 0.1% Tergitol (v/v), 4.0 mM MgSO4 and 100 mM Tricine pH 8.4. Panel A illustrates inhibition of CYP1A2 by phenacetin using Luc ME as substrate. Panel B illustrates inhibition of CYP1A1 by phenacetin using Luc CEE as substrate. Panel C illustrates inhibition of CYP2C9 by diclofenac using HLuc as substrate.

FIG. 12: P450 action on methoxy-coelenterazine HH, coelenterazine HH and coelenterazine by chemiluminescent and bioluminescent detection . Panel A shows bioluminescence from methoxy-coelenterazine-HH in relative light units (RLU) generated in a Renilla luciferase containing reaction following incubation of methoxy-coelenterazine HH with (+) or without (-) various P450 isozymes. Panel B shows the fold increase in bioluminescence from reactions containing methoxycoelenterazine HH and P450 (+P450 RLU/-P450 RLU). Panel C shows

chemiluminescence from methoxy-coelenterazine HH in RLU generated following incubation of methoxy-coelenterazine HH with (+) or without (-) various P450 isozymes. Panel D shows the fold increase in chemiluminescence from reactions containing methoxy-coelenterazine HH and P450 (+P450 RLU/-P450 RLU). Panel E shows bioluminescence from coelenterazine HH in RLU generated in a Renilla luciferase containing reaction following incubation of coelenterazine HH with (+) or without () various P450 isozymes. Panel F shows the fold decrease in bioluminescence from reactions containing coelenterazine HH and P450 (+P450 RLU/-P450 RLU). Panel G shows chemiluminescence from coelenterazine HH in RLU generated following incubation of coelenterazine HH with (+) or without (-) various P450 isozymes. Panel H shows the decrease in chemiluminescence from reactions containing coelenterazine HH and P450 (+P450 RLU/-P450 RLU). Panel I shows bioluminescence from coelenterazine in RLU generated in a Renilla luciferase containing reaction following incubation of coelenterazine with (+) or without (-) various P450 isozymes. Panel J shows the decrease in bioluminescence from reactions containing coelenterazine and P450 (+P450 RLU/P450 RLU). Panel K shows chemiluminescence from coelenterazine in RLU generated following incubation of coelenterazine with (+) or without (-) various P450 isozymes. Panel L shows the decrease in chemiluminescence from reactions containing coelenterazine and P450 (+P450 RLU/-P450 RLU).

FIG. 13. Protection of luciferase from inhibitory buffer using yeast iPPase. Yeast inorganic pyrophosphatase was found to be effective in reversing iPP inhibition of luciferase when inhibitory KPO4 buffer used.

FIG. 14. Inorganic pyrophosphatases protect luciferase from pyrophosphatase contamination. Inorganic pyrophosphatases from different sources were found to reverse iPP inhibition of luciferase when inhibitory KPO4 buffer is used.

FIG. 15. Protection of luciferase from added iPP using iPPase. Inorganic pyrophosphatase was found to be effective in reversing iPP inhibition of a luciferase-based reaction when iPP is added to the reaction.

FIG. 16. Cell-based Luminescent CYP450 Assays. Primary rat hepatocytes were treated for 2 days with inducers of CYP450 gene expression: 5 micromolar 3-methylcholanthrene (MC), 50 micromolar dexamthasone (Dex) or 50 micromolar rifampicin (Rif) and their vehicle controls, 0.05, 0.1 and 0.1% DMSO, respectively (uninduced); and an inhibitor of CYP450: 100 micromolar troleandomycin (Tro). The induction medium was then replaced with 300 microliters of 100 micromolar luciferin-CEE (panels A and B), 200 micromolar luciferin -BE or 200 micromolar luciferin-BE plus Tro dissolved in hepatocyte culture medium and allowed to incubate for 4 hours. 100 microliters of medium was then removed from wells and combined with luciferin detection reagent (see example 15) and 200 microliters of luciferin detection reagent was added to the remaining 200 microliters of medium on cells. Luminescence from 200 microliters of culture medium reactions (panels A & C) and cell lysate reactions (panels B & D) was quantified.

FIG. 17. Stabilization of luminescent signals using luciferase inhibitors. Inhibition of luciferase by an inhibitor 2-(4aminophenyl)-6-methylbenzothiazole (APMBT) or 2-amino-6-methyl benzothiazole (AMBT) stabilizes the luminescent signal in a luminescent CYP450 assay. 50 microliter CYP1A1 reactions (0.5 pmol recombinant CYP1A1 enzyme, 30 mu M Luciferin chloroethyl ether, 100 mM KPO4, 1.3 mM NADP+, 3.3 mM glucose-6-phosphate, 3. 3 mM MgCl2, 0.02 unit glucose-6-phosphate dehydrogenase) were incubated at 37 degrees C. for 20 min. After the incubation, 50 microliters of a luciferin detection

reagent (100 micrograms/mL thermostable luciferase (from Photuris pennsylvanica), 400 micromolar ATP, 0.6% Prionex, 2 units/mL iPPase, 200 mM Tricine pH 8.4, 20 mM MgSO4, 2% Tergitol) containing either 100 micromolar APMBT, 100 micromolar AMBT, or no inhibitor were added to each aliquot of CYP1A1 reaction. Luminescence was read immediately and at subsequent 5 minute intervals for 1 hour.

L8 ANSWER 17 OF 71 IFIPAT COPYRIGHT 2008 IFI on STN

AN 10654554 IFIPAT;IFIUDB;IFICDB <<LOGINID::20080318>>

TITLE: PROTEIN FRAGMENT COMPLEMENTATION ASSAYS FOR HIGH-THROUGHPUT AND HIGH-CONTENT SCREENING; USING CELL-BASED ASSAYS TO ASSESS BIOLOGICAL ACTIVITY OF CHEMICAL COMPOUNDS AND MECHANISM-OF-ACTION OF NEW BIOLOGICAL TARGETS; DRUG SCREENING

INVENTOR(S): Lamerdin; Jane, Livermore, CA, US
MacDonald; Marnie, Pleasanton, CA, US
Michnick; Stephen William Watson, Westmount, CA
Remy; Ingrid, Montreal, CA
Westwick; John K., San Ramon, CA, US
Yu; Helen, Mountain View, CA, US

PATENT ASSIGNEE(S): Odyssey Thera, Inc., San Ramon, CA, US

AGENT: Isaac A. Angres;Suite 301, 2001 Jefferson Davis Highway, Arlington, VA, 22202, US

	NUMBER	PK	DATE
PATENT INFORMATION:	US 2004161787	A1	20040819
APPLICATION INFORMATION:	US 2004-772021		20040205

	APPLN. NUMBER	DATE	GRANTED PATENT NO. OR STATUS
CONTINUATION OF:	US 1998-17412	19980202	6270964
CONTINUATION OF:	US 2000-499464	20000207	6428951
CONTINUATION OF:	US 2002-154758	20020524	PENDING
CONTINUATION-IN-PART OF:	US 2003-353090	20030129	PENDING

	NUMBER	DATE	
PRIORITY APPLN. INFO.:	CA 1997-2196496	19970131	
	US 2003-445225P	20030206	(Provisional)
FAMILY INFORMATION:	US 2004161787	20040819	
	US 6270964		
	US 6428951		

DOCUMENT TYPE: Utility
Patent Application - First Publication

FILE SEGMENT: CHEMICAL
APPLICATION

OTHER SOURCE: CA 141:168969

ENTRY DATE: Entered STN: 20 Aug 2004
Last Updated on STN: 6 Jun 2006

NUMBER OF CLAIMS: 39 24 Figure(s).

DESCRIPTION OF FIGURES:

FIG. 1 illustrates the construction of a high-throughput or highcontent assay using PCA.

FIG. 2 shows the DNA damage response pathway and shows highthroughput assays based on beta-lactamase PCA (BLA PCA) and high-content assays based on GFP (GFP PCA) for the Chk1/p53 and p53/p53 interactions. CPT=camptothecin.

FIG. 3(A) shows a luminescent PCA for HTS based on Renilla luciferase (RLuc PCA).

FIG. 3(B) shows induction of the p53/p53 interaction by camptothecin in the RLuc PCA.
FIG. 4 shows a fluorescent, high-content assay based on IFP PCA. Cell images show the inhibitory effect of Geldanamycin and the potentiating effect of Trichostatin A on the p53/p53 interaction in the absence and presence of CPT. The bar graph shows the effects of various known agents on the mean fluorescence in the cell nucleus. Legend to bar graph: 1=vehicle (DMSO); 2=Camptothecin (500 nM CPT); 3=Genistein (12. 5 micromolar); 4=Trichostatin A (0.5 micromolar); 5=MS-275 (10 micromolar); 6=LY294002 (25 micromolar); 7=SB 203580 (25 micromolar); 8=HA 14-1 (2 micromolar); 9=Geldanamycin (2.5 micromolar).
FIG. 5(A) depicts the organization of the PI-3-kinase and PKA/ PKC-mediated pathways, including a novel interaction between PKB and hFt1 that was identified by cDNA library screening using GFP PCA.
FIG. 5(B) illustrates the effects of activators and inhibitors on the quantity and subcellular locations of the PKB/hFt1 and hFt1/PDK1 complexes in living cells, as detected by a GFP PCA with fluorescence spectrometric detection. 1=COS-1 cells; 2=Jurkat cells; 3=images of COS-1 cells with PCA inside. The dimerization of GCN4/GCN4 leucine zippers was used as a control.
FIG. 6 illustrates (A) the cellular pathway leading to FRAP (FKBP-Rapamycin-Associated Protein); (B) a YFP PCA, enabling visualization of the effects of the drug rapamycin on the interaction of FKBP and mTOR (mTOR is the murine equivalent of FRAP); (C) A dose-response curve for rapamycin in the highthroughput assay.
FIG. 7(A,B) shows the quantitative results of a 96-well plate assay in which gene-by-gene interaction mapping with YFP PCA was performed to identify protein-protein interactions. Assays were read by fluorescence spectrometry.
FIG. 7(C,D) shows scanned images of wells from the high throughput interaction mapping assays of FIG. 7(A,B), including magnified images of the positive PCA control; negative PCA control; and a novel interaction. The subcellular locations of protein-protein complexes can be seen. Images were acquired by automated microscopy.
FIG. 8 illustrates the organization of the pathway leading from the TNF receptor to the cell nucleus, including the IKK (Ikappa-B-Kinase) complex; the NF-kappa-B (NFkB) transcription factor complex (p65/p50), which relocalizes to the nucleus upon TNF stimulation; the cytoplasmic I-kappa-B-alpha (IkBa)/NFkB complex; and the inhibition of NFkB signaling by proteasome inhibitors such as ALLN.
FIG. 9 shows fluorescent PCAs for numerous protein-protein complexes in the TNF pathway, demonstrating correct subcellular localization and showing that multi-color PCAs can be constructed for any protein. Membrane, cytosolic and nuclear complexes are shown from the receptor to the nucleus, and the ubiquitination of proteins is demonstrated.
FIG. 10 shows the results of a high-content PCA for NFkappaB (NFkB, p65/p50) in transiently-transfected cells, demonstrating redistribution of the protein-protein complex in response to TNF and inhibition of the TNF response by the proteasome inhibitor ALLN.
FIG. 11 shows two different stable cell lines with 'PCA inside'.
FIG. 12(A) shows the TNF dose-response curve and the time course of induction of nuclear translocation of NFkB (p65/p50) in the stable PCA cell line shown in FIG. 11.
FIG. 12(B) shows inhibition of the TNF response by the proteasome inhibitor ALLN in the stable PCA cell line shown in FIG. 11.
FIG. 12(C) shows the further use of the stable PCA cell line from FIG. 11 for high-content screening of a chemical library.
FIG. 12(D) shows a quantitative dose-response curve for a 'hit' from the chemical library screen depicted in FIG. 12(C).
FIG. 13(A) shows another high-content PCA for NFkB translocation in live cells, generating a red fluorescent signal based on DHFR PCA.
FIG. 13(B) shows that the DHFR PCA can also be used to detect inhibition of the nuclear translocation of NFkB by the proteasome inhibitor, ALLN.

FIG. 14 shows a quantitative, fluorescent, high-throughput PCA in a stable cell line for another sentinel in the TNF signaling pathway (IkBa/p65). Images show a reduction in signal in response to TNF, an effect that is blocked by the proteasome inhibitor, ALLN. Panel A shows the TNF dose-response for the IkBa/p65 PCA; Panel B showns the time-course for the TNF effect on the IkBa/p65 PCA.

FIG. 15 shows the detection and quantitation of ubiquitinprotein complexes with PCA, showing that the proteasome inhibitor ALLN increases the accumulation of ubiquitin-IkBa complexes in the presence of TNF.

FIG. 16 provides an outline of vector construction for examples of PCA vectors suitable for the present invention.

FIG. 17 provides "dual PCAs" in which the construction of an HTS or HCS assay is linked to the generation of a stable cell line. Complementary bicistronic vectors are used to generate a stable cell line, such as with a leucine zipper-directed DHFR PCA, wherein the cell line also contains a fluorescent or luminescent PCA, where the fluorescent or luminescent signal is driven by the interaction of two proteins of interest.

AB The present invention provides protein fragment complementation assays for drug discovery, in particular to identify compounds that activate or inhibit cellular pathways. Based on the selection of an interacting protein pair combined with an appropriate PCA reporter, the assays may be run in highthroughput or high-content mode and may be used in automated screening of libraries of compounds. The interacting pair may be selected by cDNA library screening; by gene-by-gene interaction mapping; or by prior knowledge of a pathway. Fluorescent and luminescent assays can be constructed using the methods provided herein. The selection of suitable PCA reporters for high-throughput or high-content (high-context) assay formats is described for a diversity of reporters, with particular detail provided for examples of monomeric enzymes and fluorescent proteins. Methods are described for constructing such assays for one or more steps in a biochemical pathway; testing the effects of compounds from combinatorial, natural product, peptide, antibody, nucleic acid or other diverse libraries on the protein or pathway(s) of interest; and using the results of the screening to identify specific compounds that activate or inhibit the protein or pathway(s) of interest. Single-color and multi-color assays are disclosed. Further disclosed are universal expression vectors with cassettes that allow the rapid construction of assays for a large and diverse number of gene/reporter combinations. The development of such assays is shown to be straightforward, providing for a broad, flexible and biologically relevant platform for drug discovery.

CLMN 39 24 Figure(s).

FIG. 1 illustrates the construction of a high-throughput or highcontent assay using PCA.

FIG. 2 shows the DNA damage response pathway and shows highthroughput assays based on beta-lactamase PCA (BLA PCA) and high-content assays based on GFP (GFP PCA) for the Chk1/p53 and p53/p53 interactions. CPT=camptothecin.

FIG. 3(A) shows a luminescent PCA for HTS based on Renilla luciferase (RLuc PCA).

FIG. 3(B) shows induction of the p53/p53 interaction by camptothecin in the RLuc PCA.

FIG. 4 shows a fluorescent, high-content assay based on IFP PCA. Cell images show the inhibitory effect of Geldanamycin and the potentiating effect of Trichostatin A on the p53/p53 interaction in the absence and presence of CPT. The bar graph shows the effects of various known agents on the mean fluorescence in the cell nucleus. Legend to bar graph: 1=vehicle (DMSO); 2=Camptothecin (500 nM CPT); 3=Genistein (12. 5 micromolar); 4=Trichostatin A (0.5 micromolar); 5=MS-275 (10 micromolar);

6=LY294002 (25 micromolar); 7=SB 203580 (25 micromolar); 8=HA 14-1 (2 micromolar); 9=Geldanamycin (2.5 micromolar).

FIG. 5(A) depicts the organization of the PI-3-kinase and PKA/PKC-mediated pathways, including a novel interaction between PKB and hFt1 that was identified by cDNA library screening using GFP PCA.

FIG. 5(B) illustrates the effects of activators and inhibitors on the quantity and subcellular locations of the PKB/hFt1 and hFt1/PDK1 complexes in living cells, as detected by a GFP PCA with fluorescence spectrometric detection. 1=COS-1 cells; 2=Jurkat cells; 3=images of COS-1 cells with PCA inside. The dimerization of GCN4/GCN4 leucine zippers was used as a control.

FIG. 6 illustrates (A) the cellular pathway leading to FRAP (FKBP-Rapamycin-Associated Protein); (B) a YFP PCA, enabling visualization of the effects of the drug rapamycin on the interaction of FKBP and mTOR (mTOR is the murine equivalent of FRAP); (C) A dose-response curve for rapamycin in the highthroughput assay.

FIG. 7(A,B) shows the quantitative results of a 96-well plate assay in which gene-by-gene interaction mapping with YFP PCA was performed to identify protein-protein interactions. Assays were read by fluorescence spectrometry.

FIG. 7(C,D) shows scanned images of wells from the high throughput interaction mapping assays of FIG. 7(A,B), including magnified images of the positive PCA control; negative PCA control; and a novel interaction. The subcellular locations of protein-protein complexes can be seen. Images were acquired by automated microscopy.

FIG. 8 illustrates the organization of the pathway leading from the TNF receptor to the cell nucleus, including the IKK (Ikappa-B-Kinase) complex; the NF-kappa-B (NFkB) transcription factor complex (p65/p50), which relocalizes to the nucleus upon TNF stimulation; the cytoplasmic I-kappa-B-alpha (IkBa)/NFkB complex; and the inhibition of NFkB signaling by proteasome inhibitors such as ALLN.

FIG. 9 shows fluorescent PCAs for numerous protein-protein complexes in the TNF pathway, demonstrating correct subcellular localization and showing that multi-color PCAs can be constructed for any protein. Membrane, cytosolic and nuclear complexes are shown from the receptor to the nucleus, and the ubiquitination of proteins is demonstrated.

FIG. 10 shows the results of a high-content PCA for NFkappaB (NFkB, p65/p50) in transiently-transfected cells, demonstrating redistribution of the protein-protein complex in response to TNF and inhibition of the TNF response by the proteasome inhibitor ALLN.

FIG. 11 shows two different stable cell lines with 'PCA inside'.

FIG. 12(A) shows the TNF dose-response curve and the time course of induction of nuclear translocation of NFkB (p65/p50) in the stable PCA cell line shown in FIG. 11.

FIG. 12(B) shows inhibition of the TNF response by the proteasome inhibitor ALLN in the stable PCA cell line shown in FIG. 11.

FIG. 12(C) shows the further use of the stable PCA cell line from FIG. 11 for high-content screening of a chemical library.

FIG. 12(D) shows a quantitative dose-response curve for a 'hit' from the chemical library screen depicted in FIG. 12(C).

FIG. 13(A) shows another high-content PCA for NFkB translocation in live cells, generating a red fluorescent signal based on DHFR PCA.

FIG. 13(B) shows that the DHFR PCA can also be used to detect inhibition of the nuclear translocation of NFkB by the proteasome inhibitor, ALLN.

FIG. 14 shows a quantitative, fluorescent, high-throughput PCA in a stable cell line for another sentinel in the TNF signaling pathway (IkBa/p65). Images show a reduction in signal in response to TNF, an effect that is blocked by the proteasome inhibitor, ALLN. Panel A shows the TNF dose-response for the IkBa/p65 PCA; Panel B showns the time-course for the TNF effect on the IkBa/p65 PCA.

FIG. 15 shows the detection and quantitation of ubiquitinprotein complexes

with PCA, showing that the proteasome inhibitor ALLN increases the accumulation of ubiquitin-IkBa complexes in the presence of TNF.

FIG. 16 provides an outline of vector construction for examples of PCA vectors suitable for the present invention.

FIG. 17 provides "dual PCAs" in which the construction of an HTS or HCS assay is linked to the generation of a stable cell line. Complementary bicistronic vectors are used to generate a stable cell line, such as with a leucine zipper-directed DHFR PCA, wherein the cell line also contains a fluorescent or luminescent PCA, where the fluorescent or luminescent signal is driven by the interaction of two proteins of interest.

L8 ANSWER 18 OF 71 USPATFULL on STN DUPLICATE 1
ACCESSION NUMBER: 2003:112942 USPATFULL <<LOGINID::20080318>>
TITLE: Immunoassay Method For The Diagnosis Of Gastric Intestinal Metaplasia Associated With Gastric Carcinoma
INVENTOR(S): Das, Kiron M, Martinsville, NJ, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003077675	A1	20030424
	US 6835549	B2	20041228
APPLICATION INFO.:	US 2000-512515	A1	20000224 (9)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: PERKINS COIE LLP, POST OFFICE BOX 1208, SEATTLE, WA, 98111-1208
NUMBER OF CLAIMS: 29
EXEMPLARY CLAIM: 1
LINE COUNT: 1097
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention pertains to an in vitro immunoassay method for diagnosing human gastric intestinal metaplasia which comprises the steps of (a) contacting a gastric tissue sample of a subject suspected of having human gastric intestinal metaplasia cells with the monoclonal antibody DAS-1, or a fragment thereof, which monoclonal antibody is produced by the hybridoma deposited under ATCC accession number HB 9397 and which reacts with human gastric intestinal metaplasia antigen; and (b) detecting immunoreactivity between the gastric tissue and the monoclonal antibody, such immunoreactivity indicating a positive diagnosis of human gastric intestinal metaplasia. This invention also pertains to an in vivo immunoassay method for diagnosing human gastric intestinal metaplasia which comprises the steps of (a) administering to a human, suspected of having human gastric intestinal metaplasia, the monoclonal antibody DAS-1, or a fragment thereof, which monoclonal antibody is produced by the hybridoma deposited under ATCC accession number HB 9397 and which reacts with human gastric intestinal metaplasia antigen and is tagged with an isotope; and (b) detecting immunoreactivity between the human gastric intestinal metaplasia cells and the monoclonal antibody by external scanning, such immunoreactivity indicating a positive diagnosis of human gastric intestinal metaplasia.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 19 OF 71 USPATFULL on STN
ACCESSION NUMBER: 2003:324628 USPATFULL <<LOGINID::20080318>>
TITLE: Compositions selective for caffeine or aspartame and methods of using same
INVENTOR(S): Cload, Sharon T., Cambridge, MA, UNITED STATES
Ferguson, Alicia, Somerville, MA, UNITED STATES

	NUMBER	KIND	DATE

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003228603	A1	20031211
APPLICATION INFO.:	US 2003-406903	A1	20030403 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-370266P	20020405 (60)
	US 2002-398858P	20020725 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MINTZ, LEVIN, COHN, FERRIS, GLOVSKY, AND POPEO, P.C., ONE FINANCIAL CENTER, BOSTON, MA, 02111
NUMBER OF CLAIMS: 48
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 48 Drawing Page(s)
LINE COUNT: 4998
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compositions which recognize and report on the concentration of caffeine or aspartame target molecules. The invention further relates to methods of using the compositions to monitor the presence or concentration of such targets in a variety of samples, including those samples to be ingested, such as beverages, e.g., coffee or soft drinks.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 20 OF 71 USPATFULL on STN
ACCESSION NUMBER: 2003:306483 USPATFULL <<LOGINID::20080318>>
TITLE: Assay for evaluation of activity of compounds against HCV using a novel detection system in the HCV replicon
INVENTOR(S): Huang, Mingjun, Potomac, MD, UNITED STATES
Sun, Yongnian, Hamden, CT, UNITED STATES
Yang, Wengang, Cheshire, CT, UNITED STATES
Zhao, Yongsen, Branford, CT, UNITED STATES
Fabrycki, Joanne, Southington, CT, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003215917	A1	20031120
APPLICATION INFO.:	US 2003-407066	A1	20030403 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-369923P	20020404 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HALE AND DORR, LLP, 60 STATE STREET, BOSTON, MA, 02109
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Page(s)
LINE COUNT: 1396
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to a cell-based HTS assay for evaluation of antiviral activity of compounds against HCV using HCV replicon.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 21 OF 71 USPATFULL on STN
ACCESSION NUMBER: 2003:288600 USPATFULL <<LOGINID::20080318>>
TITLE: Exogenous nucleic acid detection
INVENTOR(S): Shultz, John William, Verona, WI, UNITED STATES
Lewis, Martin K., Madison, WI, UNITED STATES

Leippe, Donna, Madison, WI, UNITED STATES
Mandrekar, Michelle, Oregon, WI, UNITED STATES
Kephart, Daniel, Cottage Grove, WI, UNITED STATES
Rhodes, Richard Byron, Madison, WI, UNITED STATES
Andrews, Christine Ann, Cottage Grove, WI, UNITED STATES
Hartnett, James Robert, Madison, WI, UNITED STATES
Gu, Trent, Madison, WI, UNITED STATES
Olson, Ryan J., Madison, WI, UNITED STATES
Wood, Keith V., Madison, WI, UNITED STATES
Welch, Roy, Palo Alto, CA, UNITED STATES

PATENT ASSIGNEE(S): Promega Corporation, Madison, WI, UNITED STATES, 53711 (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003203358	A1	20031030
APPLICATION INFO.:	US 2001-780863	A1	20010209 (9)

RELATED APPLN. INFO.: Division of Ser. No. US 1999-406147, filed on 27 Sep 1999, GRANTED, Pat. No. US 6270974 Continuation-in-part of Ser. No. US 1999-358972, filed on 21 Jul 1999, GRANTED, Pat. No. US 6235480 Continuation-in-part of Ser. No. US 1999-252436, filed on 18 Feb 1999, GRANTED, Pat. No. US 6159693 Continuation-in-part of Ser. No. US 1998-42287, filed on 13 Mar 1998, GRANTED, Pat. No. US 6335162
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: WELSH & KATZ, LTD, 120 S RIVERSIDE PLAZA, 22ND FLOOR, CHICAGO, IL, 60606
NUMBER OF CLAIMS: 57
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 4758
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Processes are disclosed using the depolymerization of a nucleic acid hybrid to qualitatively and quantitatively analyze for the presence of a predetermined exogenous nucleic acid. Applications of those processes include the detection of single nucleotide polymorphisms, identification of single base changes, determination of viral load, genotyping, medical marker diagnostics, and the like.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 22 OF 71 USPATFULL on STN
ACCESSION NUMBER: 2003:237907 USPATFULL <<LOGINID::20080318>>
TITLE: Compositions and methods for the therapy and diagnosis of colon cancer
INVENTOR(S): King, Gordon E., Shoreline, WA, UNITED STATES
Meagher, Madeleine Joy, Seattle, WA, UNITED STATES
Xu, Jiangchun, Bellevue, WA, UNITED STATES
Secrist, Heather, Seattle, WA, UNITED STATES
Jiang, Yuqiu, Kent, WA, UNITED STATES
PATENT ASSIGNEE(S): Corixa Corporation, Seattle, WA, UNITED STATES, 98104 (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003166064	A1	20030904
APPLICATION INFO.:	US 2002-99926	A1	20020314 (10)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2001-33528, filed

on 26 Dec 2001, PENDING Continuation-in-part of Ser. No. US 2001-920300, filed on 31 Jul 2001, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-302051P	20010629 (60)
	US 2001-279763P	20010328 (60)
	US 2000-223283P	20000803 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: SEED INTELLECTUAL PROPERTY LAW GROUP PLLC, 701 FIFTH AVE, SUITE 6300, SEATTLE, WA, 98104-7092
NUMBER OF CLAIMS: 17
EXEMPLARY CLAIM: 1
LINE COUNT: 8531
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compositions and methods for the therapy and diagnosis of cancer, particularly colon cancer, are disclosed. Illustrative compositions comprise one or more colon tumor polypeptides, immunogenic portions thereof, polynucleotides that encode such polypeptides, antigen presenting cell that expresses such polypeptides, and T cells that are specific for cells expressing such polypeptides. The disclosed compositions are useful, for example, in the diagnosis, prevention and/or treatment of diseases, particularly colon cancer.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 23 OF 71 USPATFULL on STN
ACCESSION NUMBER: 2003:173153 USPATFULL <<LOGINID::20080318>>
TITLE: Human cDNAs and proteins and uses thereof
INVENTOR(S): Bejanin, Stephane, Paris, FRANCE
Tanaka, Hiroaki, Antony, FRANCE
PATENT ASSIGNEE(S): GENSET, S.A., Paris, FRANCE, 75008 (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003118997	A1	20030626
APPLICATION INFO.:	US 2001-978418	A1	20011015 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-311305P	20010810 (60)
	US 2001-314734P	20010824 (60)
	US 2001-318204P	20010907 (60)
	US 2001-326470P	20011001 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Saliwanchik, Lloyd & Saliwanchik, Frank C. Eisenchenk, Ph. D, 2421 N.W. 41st street, Suite A-1, Gainesville, FL, 32606-6669
NUMBER OF CLAIMS: 13
EXEMPLARY CLAIM: 1
LINE COUNT: 15316
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention concerns GENSET polynucleotides and polypeptides. Such GENSET products may be used as reagents in forensic analyses, as chromosome markers, as tissue/cell/organelle-specific markers, in the production of expression vectors. In addition, they may be used in screening and diagnosis assays for abnormal GENSET expression and/or biological activity and for screening compounds that may be used in the

treatment of GENSET-related disorders.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 24 OF 71 USPATFULL on STN
ACCESSION NUMBER: 2003:159444 USPATFULL <<LOGINID::20080318>>
TITLE: Apparatus and methods for chemiluminescent assays
INVENTOR(S): DiCesare, Joseph L., Redding, CT, UNITED STATES
McCaffrey, John T., Cheshire, CT, UNITED STATES
Clark, David, Sandy Hook, CT, UNITED STATES
Crockett, Michael I., Newtown, CT, UNITED STATES
PATENT ASSIGNEE(S): Neogen Corporation, Lansing, MI (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003109057	A1	20030612
APPLICATION INFO.:	US 2002-326332	A1	20021219 (10)

RELATED APPLN. INFO.: Division of Ser. No. US 2001-821148, filed on 29 Mar 2001, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-193519P	20000331 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MCLEOD MOYNE & REILLY, P.C., 2190 COMMONS PARKWAY, OKEMOS, MI, 48864
NUMBER OF CLAIMS: 40
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 6 Drawing Page(s)
LINE COUNT: 1666
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Disclosed herein is a device and methods for the rapid chemiluminescence assay of surfaces to detect the presence of microbial contamination. The device and methods are suitable for use by untrained personnel under the relatively harsh and variable conditions found in the field, for example in fast food restaurants and other food preparation areas. The chemiluminescence reaction that is the source of the analytical signal in the disclosed assay device and method is preferably based on a luciferase/luciferin system. The method for sampling disclosed herein comprises the steps of pre-wetting the sampling swab to a level below that of absorptive saturation; wiping a surface to be sampled with the swab with sufficient pressure to expel the wetting solution onto the surface; and, after reducing the pressure exerted on the sampling swab, further wiping the surface to re-absorb the moisture from the surface.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 25 OF 71 USPATFULL on STN
ACCESSION NUMBER: 2003:159373 USPATFULL <<LOGINID::20080318>>
TITLE: Compositions and methods comprising G-protein coupled receptors
INVENTOR(S): Communi, Didier, Dilbeek, BELGIUM
Lannoy, Vincent, Brussels, BELGIUM
Brezillon, Stephane, Brussels, BELGIUM
Detheux, Michel, Mons, BELGIUM
Parmentier, Marc, Brussels, BELGIUM
Govaerts, Cedric, Brussels, BELGIUM
PATENT ASSIGNEE(S): Euroscreen, S.A. (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003108986	A1	20030612
APPLICATION INFO.:	US 2002-79384	A1	20020220 (10)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2001-885453, filed on 21 Jun 2001, PENDING
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: PALMER & DODGE, LLP, KATHLEEN M. WILLIAMS, 111 HUNTINGTON AVENUE, BOSTON, MA, 02199
NUMBER OF CLAIMS: 54
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 29 Drawing Page(s)
LINE COUNT: 5021
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to G-protein coupled receptors and the nucleic acid molecules encoding them. The invention further relates to methods of screening for compounds which modulate the activity of one or more of the G-protein coupled receptors disclosed herein, and methods for modulating receptor activity. The invention also provides a natural ligand for one or more of the G-protein coupled receptors disclosed herein, and methods for identifying other natural ligands for these receptors.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 26 OF 71 USPATFULL on STN
ACCESSION NUMBER: 2003:127865 USPATFULL <<LOGINID::20080318>>
TITLE: Receptor GPCRx10
INVENTOR(S): Communi, Didier, Vilvorde, BELGIUM
Lannoy, Vincent, Brussels, BELGIUM
Govaerts, Cedric, Brussels, BELGIUM
Parmentier, Marc, Brussels, BELGIUM
Detheux, Michel, Mons, BELGIUM

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003088080	A1	20030508
APPLICATION INFO.:	US 2001-885453	A1	20010621 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	EP 2000-870289	20001205
	US 2000-212908P	20000620 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: PALMER & DODGE, LLP, KATHLEEN M. WILLIAMS / STR, 111 HUNTINGTON AVENUE, BOSTON, MA, 02199
NUMBER OF CLAIMS: 18
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Page(s)
LINE COUNT: 1713
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention is related to a novel G-protein coupled receptor having an amino acid sequence which presents more than 75% sequence identity with the sequence SEQ ID NO. 1. The present invention further comprises a method for screening a substance as a potential agonist, reverse agonist, or antagonist to the receptor of the invention. The present invention further comprises a diagnostic method to identify expression of the receptor in target tissues or cells.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 27 OF 71 USPATFULL on STN
ACCESSION NUMBER: 2003:106233 USPATFULL <<LOGINID::20080318>>
TITLE: Compositions and methods for the therapy and diagnosis of pancreatic cancer
INVENTOR(S): Benson, Darin R., Seattle, WA, UNITED STATES
Kalos, Michael D., Seattle, WA, UNITED STATES
Lodes, Michael J., Seattle, WA, UNITED STATES
Persing, David H., Redmond, WA, UNITED STATES
Hepler, William T., Seattle, WA, UNITED STATES
Jiang, Yuqiu, Kent, WA, UNITED STATES
PATENT ASSIGNEE(S): Corixa Corporation, Seattle, WA, UNITED STATES, 98104 (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003073144	A1	20030417
APPLICATION INFO.:	US 2002-60036	A1	20020130 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-333626P	20011127 (60)
	US 2001-305484P	20010712 (60)
	US 2001-265305P	20010130 (60)
	US 2001-267568P	20010209 (60)
	US 2001-313999P	20010820 (60)
	US 2001-291631P	20010516 (60)
	US 2001-287112P	20010428 (60)
	US 2001-278651P	20010321 (60)
	US 2001-265682P	20010131 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: SEED INTELLECTUAL PROPERTY LAW GROUP PLLC, 701 FIFTH AVE, SUITE 6300, SEATTLE, WA, 98104-7092
NUMBER OF CLAIMS: 17
EXEMPLARY CLAIM: 1
LINE COUNT: 14253
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Compositions and methods for the therapy and diagnosis of cancer, particularly pancreatic cancer, are disclosed. Illustrative compositions comprise one or more pancreatic tumor polypeptides, immunogenic portions thereof, polynucleotides that encode such polypeptides, antigen presenting cell that expresses such polypeptides, and T cells that are specific for cells expressing such polypeptides. The disclosed compositions are useful, for example, in the diagnosis, prevention and/or treatment of diseases, particularly pancreatic cancer.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 28 OF 71 USPATFULL on STN
ACCESSION NUMBER: 2003:99724 USPATFULL <<LOGINID::20080318>>
TITLE: Proteins and druggable regions of proteins
INVENTOR(S): Edwards, Aled, Toronto, CANADA
Arrowsmith, Cheryl, North York, CANADA
Greenblatt, Jack, Toronto, CANADA
Mendlein, John D., Encincitas, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003068831	A1	20030410

APPLICATION INFO.: US 2002-97125 A1 20020312 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-275216P	20010312 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: FOLEY HOAG LLP, PATENT GROUP, WORLD TRADE CENTER WEST, 155 SEAPORT BOULEVARD, BOSTON, MA, 02110-2600
NUMBER OF CLAIMS: 31
EXEMPLARY CLAIM: 1
LINE COUNT: 4944
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to methods for learning structural information about a molecule or molecular complex. The invention also provides methods for identifying a compound that binds to a molecule or molecular complex. The invention also provides methods for identifying a compound that binds to one molecule or molecular complex and not to one or more other molecules or molecular complexes. Other methods that are provided can be used to identify a compound that binds to at least two molecules or molecular complexes.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 29 OF 71 USPATFULL on STN
ACCESSION NUMBER: 2003:99546 USPATFULL <<LOGINID::20080318>>
TITLE: Multi-target analysis of gene families for chemistry of high affinity and selective small molecules and other therapeutics
INVENTOR(S): Arrowsmith, Cheryl, North York, CANADA
Greenblatt, Jack, Toronto, CANADA
Edwards, Aled, Toronto, CANADA
Mendlein, John D., Encincitas, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003068651	A1	20030410
APPLICATION INFO.:	US 2002-97194	A1	20020312 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-275216P	20010312 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: FOLEY HOAG LLP, PATENT GROUP, WORLD TRADE CENTER WEST, 155 SEAPORT BOULEVARD, BOSTON, MA, 02110-2600
NUMBER OF CLAIMS: 79
EXEMPLARY CLAIM: 1
LINE COUNT: 5161
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to methods for learning structural information about a molecule or molecular complex. The invention also provides methods for identifying a compound that binds to a molecule or molecular complex. The invention also provides methods for identifying a compound that binds to one molecule or molecular complex and not to one or more other molecules or molecular complexes. Other methods that are provided can be used to identify a compound that binds to at least two molecules or molecular complexes.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 30 OF 71 USPATFULL on STN
ACCESSION NUMBER: 2003:99545 USPATFULL <<LOGINID::20080318>>
TITLE: Target analysis for chemistry of specific and broad spectrum anti-infectives and other therapeutics
INVENTOR(S): Greenblatt, Jack, Toronto, CANADA
Edwards, Aled, Toronto, CANADA
Arrowsmith, Cheryl, North York, CANADA
Mendlein, John D., Encincitas, CA, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003068650	A1	20030410	
APPLICATION INFO.:	US 2002-97193	A1	20020312	(10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-275216P	20010312 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: FOLEY HOAG LLP, PATENT GROUP, WORLD TRADE CENTER WEST, 155 SEAPORT BOULEVARD, BOSTON, MA, 02110-2600
NUMBER OF CLAIMS: 52
EXEMPLARY CLAIM: 1
LINE COUNT: 5051
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to methods for learning structural information about a molecule or molecular complex. The invention also provides methods for identifying a compound that binds to a molecule or molecular complex. The invention also provides methods for identifying a compound that binds to one molecule or molecular complex and not to one or more other molecules or molecular complexes. Other methods that are provided can be used to identify a compound that binds to at least two molecules or molecular complexes.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 31 OF 71 USPATFULL on STN
ACCESSION NUMBER: 2003:51240 USPATFULL <<LOGINID::20080318>>
TITLE: Recombinant constructs and their use in reducing gene expression
INVENTOR(S): Glassman, Kimberly F., Ankeny, IA, UNITED STATES
Gordon-Kamm, William J., Urbandale, IA, UNITED STATES
Kinney, Anthony J., Wilmington, DE, UNITED STATES
Lowe, Keith S., Johnston, IA, UNITED STATES
Nichols, Scott E., West Chester, PA, UNITED STATES
Stecca, Kevin L., Bear, DE, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003036197	A1	20030220	
APPLICATION INFO.:	US 2001-887194	A1	20010622	(9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-213961P	20000623 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: E I DU PONT DE NEMOURS AND COMPANY, LEGAL PATENT RECORDS CENTER, BARLEY MILL PLAZA 25/1128, 4417 LANCASTER PIKE, WILMINGTON, DE, 19805
NUMBER OF CLAIMS: 45

EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 2765
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Recombinant constructs useful for reducing the expression of endogenous mRNA and any substantially similar endogenous mRNA are disclosed. In particular, a recombinant construct comprising, inter alia, a suitable nucleic acid sequence and its reverse complement can be used to alter the expression of any homologous, endogenous RNA (i.e., the target RNA) which is in proximity to this suitable nucleic acid sequence.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 32 OF 71 USPATFULL on STN
ACCESSION NUMBER: 2003:30303 USPATFULL <<LOGINID::20080318>>
TITLE: Functional IgE test methods and compositions
INVENTOR(S): Dreskin, Stephen C., Denver, CO, UNITED STATES
Dibbern, Donald A., JR., Tigard, OR, UNITED STATES
Williams, Phillip B., Olathe, KS, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003022250	A1	20030130	
APPLICATION INFO.:	US 2002-158568	A1	20020529	(10)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2001-294465P	20010529	(60)
	US 2001-294466P	20010529	(60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: GREENLEE, WINNER AND SULLIVAN, P.C., Suite 201, 5370 Manhattan Circle, Boulder, CO, 80303
NUMBER OF CLAIMS: 30
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Page(s)
LINE COUNT: 878
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present assays provide ex vivo methods for determining a significant and potentially life threatening response of mast cells and/or basophils of a patient to one or more antigens, where the response is mediated by IgE and the FcεRI protein binding and serotonin, histamine or other signaling or mediator of IgE-allergen binding. Cells which express IgE and FcεRI are labeled by uptake of detectable 5-hydroxytryptamine (serotonin) or other signaling compound, and the release of the intracellular pool of detectable compound is triggered by the addition of the allergen to which sensitivity is observed. Significant release in response to a particular compound or composition indicates that there is potentially danger to the patient from whom the cells were prepared if that patient comes in contact with the allergen. The assay can also be manipulated to detect the presence of a potentially dangerous allergen in a composition. Significant release of the detectable signaling compound, especially radiolabeled 5-HT, in response to a composition or compound indicates that there is the potential for a dangerous response to the composition or particular allergen.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 33 OF 71 USPATFULL on STN
ACCESSION NUMBER: 2003:4083 USPATFULL <<LOGINID::20080318>>

TITLE: Nucleotide triphosphates and their incorporation into oligonucleotides

INVENTOR(S): Beigelman, Leonid, Longmont, CO, UNITED STATES
Burgin, Alex, San Diego, CA, UNITED STATES
Beaudry, Amber, Denver, CO, UNITED STATES
Karpeisky, Alexander, Lafayette, CO, UNITED STATES
Matulic-Adamic, Jasenka, Boulder, CO, UNITED STATES
Sweedler, David, Louisville, CO, UNITED STATES
Zinnen, Shawn, Denver, CO, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003004122	A1	20030102
APPLICATION INFO.:	US 2001-825805	A1	20010404 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2000-578223, filed on 23 May 2000, PENDING Continuation-in-part of Ser. No. US 1999-476387, filed on 30 Dec 1999, PENDING Continuation-in-part of Ser. No. US 1999-474432, filed on 29 Dec 1999, PENDING Continuation-in-part of Ser. No. US 1999-301511, filed on 28 Apr 1999, PENDING Continuation-in-part of Ser. No. US 1998-186675, filed on 4 Nov 1998, GRANTED, Pat. No. US 6127535

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-83727P	19980429 (60)
	US 1997-64866P	19971105 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MCDONNELL BOEHNEN HULBERT & BERGHOFF, 300 SOUTH WACKER DRIVE, SUITE 3200, CHICAGO, IL, 60606
NUMBER OF CLAIMS: 90
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 33 Drawing Page(s)
LINE COUNT: 5252
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to novel nucleotide triphosphates, methods of synthesis and process of incorporating these nucleotide triphosphates into oligonucleotides, and isolation of novel nucleic acid catalysts (e.g., ribozymes or DNAzymes). Also, provided are the use of novel enzymatic nucleic acid molecules to inhibit HER2/neu/ErbB2 gene expression and their applications in human therapy.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 34 OF 71 USPATFULL on STN
ACCESSION NUMBER: 2003:240449 USPATFULL <<LOGINID::20080318>>
TITLE: Oligoribonucleotides with enzymatic activity

INVENTOR(S): Beigelman, Leonid, Broomfield, CO, United States
Burgin, Alex B., Chula Vista, CA, United States
Beaudry, Amber, Broomfield, CO, United States
Karpeisky, Alexander, Lafayette, CO, United States
Matulic-Adamic, Jasenka, Boulder, CO, United States
Sweedler, David, Louisville, CO, United States
Zinnen, Shawn, Denver, CO, United States

PATENT ASSIGNEE(S): Sirna Therapeutics, Inc., Boulder, CO, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6617438	B1	20030909

APPLICATION INFO.: US 1999-476387 19991230 (9)
RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1999-474432, filed on 29 Dec 1999, now patented, Pat. No. US 6528640
Continuation-in-part of Ser. No. US 1999-301511, filed on 28 Apr 1999, now patented, Pat. No. US 6482932
Continuation-in-part of Ser. No. US 1998-186675, filed on 4 Nov 1998, now patented, Pat. No. US 6127535

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-83727P	19980429 (60)
	US 1997-64866P	19971105 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Wilson, James O.
ASSISTANT EXAMINER: Crane, L E
LEGAL REPRESENTATIVE: McDonnell Boehnen Hulbert & Berghoff
NUMBER OF CLAIMS: 27
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 22 Drawing Figure(s); 21 Drawing Page(s)
LINE COUNT: 4484
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Novel nucleotide triphosphates, methods of synthesis and process of incorporating these nucleotide triphosphates into oligonucleotides, and isolation of novel nucleic acid catalysts (e.g., ribozymes) are disclosed. Also, described are the use of novel enzymatic nucleic acid molecules to inhibit HER2/neu/ErbB2 gene expression and their applications in human therapy.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 35 OF 71 USPATFULL on STN
ACCESSION NUMBER: 2003:209932 USPATFULL <<LOGINID::20080318>>
TITLE: Multiple reporter gene assay
INVENTOR(S): Bronstein, Irena Y., Newton, MA, United States
Fortin, John J., Georgetown, MA, United States
Martin, Chris S., Belmont, MA, United States
Voyta, John C., Sudbury, MA, United States
PATENT ASSIGNEE(S): Tropix, Inc., Bedford, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6602658	B1	20030805
APPLICATION INFO.:	US 1999-296540		19990422 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1995-579787, filed on 28 Dec 1995
DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Horlick, Kenneth R.
LEGAL REPRESENTATIVE: Piper Rudnick LLP, Kelber, Steven B.
NUMBER OF CLAIMS: 6
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 3 Drawing Figure(s); 3 Drawing Page(s)
LINE COUNT: 1100
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method of measuring the activity of at least two reporter gene products in an aliquot of a sample extract is disclosed. The activities of a first and second reporter enzyme are quantified by measuring the light signal produced by degradation of a first substrate by the first reporter enzyme and the light signal produced by the degradation of a

second substrate by a second reporter enzyme. Both quantifications are sequentially performed on the same aliquot of sample extract.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d L8 ibib abs 36-71

L8 ANSWER 36 OF 71 USPATFULL on STN

ACCESSION NUMBER:	2003:209931 USPATFULL <<LOGINID::20080318>>
TITLE:	Multiple reporter gene assay
INVENTOR(S):	Bronstein, Irena Y., Newton, MA, United States Fortin, John J., Georgetown, MA, United States Martin, Chris S., Belmont, MA, United States Voyta, John C., Sudbury, MA, United States
PATENT ASSIGNEE(S):	Tropix, Inc., Bedford, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6602657	B1	20030805
APPLICATION INFO.:	US 1995-579787		19951228 (8)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	GRANTED
PRIMARY EXAMINER:	Horlick, Kenneth R.
LEGAL REPRESENTATIVE:	Piper Rudnick LLP, Kelber, Steven B.
NUMBER OF CLAIMS:	40
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	0 Drawing Figure(s); 0 Drawing Page(s)
LINE COUNT:	1250

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method of measuring the activity of at least two reporter gene products in an aliquot of a sample extract is disclosed. The activities of a first and second reporter enzyme are quantified by measuring the light signal produced by degradation of a first substrate by the first reporter enzyme and the light signal produced by the degradation of a second substrate by a second reporter enzyme. Both quantifications are sequentially performed on the same aliquot of sample extract.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 37 OF 71 USPATFULL on STN

ACCESSION NUMBER:	2003:60295 USPATFULL <<LOGINID::20080318>>
TITLE:	Synthetic ribonucleic acids with RNAse activity
INVENTOR(S):	Beigelman, Leonid, Broomfield, CO, United States Burgin, Alex, Chula Vista, CA, United States Beaudry, Amber, Broomfield, CO, United States Karpeisky, Alexander, Lafayette, CO, United States Matulic-Adamic, Jasenka, Boulder, CO, United States Sweedler, David, Louisville, CO, United States Zinnen, Shawn, Denver, CO, United States
PATENT ASSIGNEE(S):	Ribozyme Pharmaceuticals, incorporated, Boulder, CO, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6528640	B1	20030304
APPLICATION INFO.:	US 1999-474432		19991229 (9)

RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1999-301511, filed on 28 Apr 1999 Continuation-in-part of Ser. No. US 1998-186675, filed on 4 Nov 1998, now patented, Pat.

No. US 6127535

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-83727P	19980429 (60)
	US 1997-64866P	19971105 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Geist, Gary
ASSISTANT EXAMINER: Crane, L. E.
LEGAL REPRESENTATIVE: McDonnell Boehnen Hulbert & Berghoff
NUMBER OF CLAIMS: 3
EXEMPLARY CLAIM: 1,2
NUMBER OF DRAWINGS: 23 Drawing Figure(s); 21 Drawing Page(s)
LINE COUNT: 3964
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Novel nucleotide triphosphates, methods of synthesis and process of incorporating these nucleotide triphosphates into oligonucleotides, and isolation of novel nucleic acid catalysts (e.g., ribozymes) are disclosed. Also, described are the use of novel enzymatic nucleic acid molecules to inhibit HER2/neu/ErbB2 gene expression and their applications in human therapy.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 38 OF 71 USPATFULL on STN
ACCESSION NUMBER: 2003:53668 USPATFULL <<LOGINID::20080318>>
TITLE: Analytical method using multiple virus labelling
INVENTOR(S): Wilson, Stuart Mark, London, UNITED KINGDOM
PATENT ASSIGNEE(S): Microsens Biophage Limited, UNITED KINGDOM (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6524809	B1	20030225	
	WO 9963348		19991209	
APPLICATION INFO.:	US 2000-701857		20001201	(9)
	WO 1999-GB1636		19990604	

	NUMBER	DATE
PRIORITY INFORMATION:	GB 1998-11977	19980604
	GB 1999-1132	19990120

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Park, Hankyel T.
LEGAL REPRESENTATIVE: Bourque & Associates, PA
NUMBER OF CLAIMS: 23
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 0 Drawing Figure(s); 0 Drawing Page(s)
LINE COUNT: 959
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to a method for detecting a target material in a sample, which method comprises the steps of: a) exposing a sample, expected to contain that target material, to at least two viruses which are capable of binding directly or indirectly with that target material so as to form a virally bound target material and to endow the virally bound target material with a distinctive property; and b) cultivating the product from stage a in the presence of an indicator material to which the viruses carried by the virally bound target material attach so as to cause the indicator material to adopt the

distinctive property of the virally bound target material; and c) monitoring the presence or otherwise of virally attached indicator material. The invention also provides a kit for use in the method of the invention.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 39 OF 71 IFIPAT COPYRIGHT 2008 IFI on STN

AN	10309935 IFIPAT;IFIUDB;IFICDB <<LOGINID::20080318>>
TITLE:	LATROPHILIN POLYNUCLEOTIDES; NUCLEOTIDE SEQUENCES CODING POLYPEPTIDE FOR USE IN THE TREATMENT OF VISION DEFECTS
INVENTOR(S):	Richards; Julia E., Ann Arbor, MI, US Rozsa; Frank W., Chelsea, MI, US
PATENT ASSIGNEE(S):	The Regents of the University of Michigan, US
AGENT:	MEDLEN & CARROLL, LLP, 101 HOWARD STREET, SUITE 350, SAN FRANCISCO, CA, 94105, US

	NUMBER	PK	DATE
PATENT INFORMATION:	US 2003054347	A1	20030320
APPLICATION INFORMATION:	US 2001-844653		20010427
FAMILY INFORMATION:	US 2003054347		20030320

DOCUMENT TYPE:	Utility Patent Application - First Publication
FILE SEGMENT:	CHEMICAL APPLICATION
OTHER SOURCE:	CA 138:217831
ENTRY DATE:	Entered STN: 28 Mar 2003 Last Updated on STN: 10 Mar 2004

GOVERNMENT INTEREST:

(0001) The present application was funded in part with government support under grant number C033662, from the National Eye Institute at the National Institutes of Health. The government has certain rights in this invention.

NUMBER OF CLAIMS: 23 82 Figure(s).

DESCRIPTION OF FIGURES:

FIG. 1 shows the cDNA nucleic acid sequence of human LPH3 (SEQ ID NO:1).
FIG. 2 shows the cDNA nucleic acid sequence of human LPH3 with additional 5' and 3' flanking regions (SEQ ID NO:2).
FIG. 3 shows a sequence alignment between the cDNA sequence of human LPH3 (SEQ ID NO:1), and accession Nos. AF307080 (human LEC3) and AB018311.
FIG. 4 shows both the nucleotide (SEQ ID NO:1) and peptide (SEQ ID NO:3) sequences of human LPH3.
FIG. 5 shows the amino acid sequence of human LPH3 (SEQ ID NO:3) and the amino acid sequence of human LEC3 (SEQ ID NO:4, accession no. AF307080).
FIG. 6 shows the exon regions of human genomic LPH3 shown in SEQ ID NO:5.
FIG. 7 shows the human genomic sequence of human LPH3 (SEQ ID NO:5), with the intronic/non-coding regions in lower case, and the exon regions shown in uppercase and bold.
FIG. 8 shows the exon regions of human genomic LPH1 shown in SEQ ID NO:32.
FIG. 9 shows the human genomic sequence of human LPH1 (SEQ ID NO:32), with the intronic/non-coding regions in lower case, and the exon regions shown in uppercase and bold.
FIG. 10 shows a hypothetical model of LPH-TIGR interaction. Importantly, the present invention is not limited to a particular mechanism of action. Indeed, an understanding of the mechanism of action is not necessary to practice the present invention. Nevertheless, this figure depicts a hypothetical model of LPH-TIGR interaction.
FIG. 11 shows the cDNA sequence of human TIGR/myocilin (SEQ ID NO:172,

accession no. NM-000261), and the amino acid sequence of human TIGR/myocilin (SEQ ID NO:173, accession no. NP-000252. Nucleotides 758-1528 of SEQ ID NO:172 encode an olfactomedin domain, and amino acids 246-502 of SEQ ID NO:173 represent an olfactomedin domain of the human TIGR peptide.

Definitions

To facilitate an understanding of the invention, a number of terms are defined below.

As used herein, the terms "subject" and "patient" refer to any animal, such as a mammal like a dog, cat, bird, livestock, and preferably a human. Specific examples of "subjects" and "patients" include, but are not limited to, individuals with glaucoma, individuals with glaucoma-related characteristics such as ocular hypertension, relatives of such individuals, and individuals at risk of glaucoma (e.g. individuals with a family history of glaucoma, and individuals over the age of 40).

As used herein, the term "eye disease" refers to diseases affecting all, or a portion of the eye, including, but not limited to, Primary Open-Angle Glaucoma (e.g. juvenile onset and adult onset), occular hypertension, and other eye diseases where, for example, the intraocular pressure is elevated.

The term "LPH gene" refers to a full-length LPH nucleotide sequence (e.g., SEQ ID NO:5 for LPH3, and SEQ ID NO:32 for LPH1) . However, it is also intended that the term encompass fragments of the genomic LPH sequences, the cDNA sequences (e.g. SEQ ID NO:1) as well as other domains within the full-length LPH nucleotide sequences. Furthermore, the terms "LPH nucleotide sequence" or "LPH polynucleotide sequence" encompasses DNA, cDNA, and RNA (e.g., MRNA) sequences.

In addition to containing introns, genomic forms of a gene may also include sequences located on both the 5' and 3' end of the sequences that are present on the RNA transcript. These sequences are referred to as "flanking" sequences or regions (these flanking sequences are located 5' or 3' to the nontranslated sequences present on the mRNA transcript). The 5' flanking region may contain regulatory sequences such as promoters and enhancers that control or influence the transcription of the gene. The 3' flanking region may contain sequences that direct the termination of transcription, posttranscriptional cleavage and polyadenylation.

Where "amino acid sequence" is recited herein to refer to an amino acid sequence of a naturally occurring protein molecule, "amino acid sequence" and like terms, such as "polypeptide" or "protein" are not meant to limit the amino acid sequence to the complete, native amino acid sequence associated with the recited protein molecule.

The term "wild-type" refers to a gene or gene product that has the characteristics of that gene or gene product when isolated from a naturally occurring source. A wild-type gene is that which is most frequently observed in a population and is thus arbitrarily designed the "normal" or "wild-type" form of the gene. In contrast, the term "variant" refers to a gene or gene product that displays modifications in sequence and/or functional properties (i.e., altered characteristics) when compared to the wild-type gene or gene product. Examples of variants include, but are not limted to, polymorphisms and mutations. It is noted that naturally-occurring mutants can be isolated; these are identified by the fact that they have altered characteristics when compared to the wild-type gene or gene product.

As used herein, the terms "nucleic acid molecule encoding," "DNA sequence encoding," and "DNA encoding" refer to the order or sequence of deoxyribonucleotides along a strand of deoxyribonucleic acid. The order of these deoxyribonucleotides determines the order of amino acids along the polypeptide (protein) chain. The DNA sequence thus codes for the amino acid sequence.

DNA molecules are said to have "5' ends" and "3' ends" because mononucleotides are reacted to make oligonucleotides or polynucleotides in a manner such that the 5' phosphate of one mononucleotide pentose ring is attached to the 3' oxygen of its neighbor in one direction via a phosphodiester linkage. Therefore, an end of an oligonucleotides or polynucleotide, referred to as the

"5' end" if its 5' phosphate is not linked to the 3' oxygen of a mononucleotide pentose ring and as the "3' end" if its 3' oxygen is not linked to a 5' phosphate of a subsequent mononucleotide pentose ring. As used herein, a nucleic acid sequence, even if internal to a larger oligonucleotide or polynucleotide, also may be said to have 5' and 3' ends. In either a linear or circular DNA molecule, discrete elements are referred to as being "upstream" or 5' of the "downstream" or 3' elements. This terminology reflects the fact that transcription proceeds in a 5' to 3' fashion along the DNA strand. The promoter and enhancer elements that direct transcription of a linked gene are generally located 5' or upstream of the coding region. However, enhancer elements can exert their effect even when located 3' of the promoter element and the coding region. Transcription termination and polyadenylation signals are located 3' or downstream of the coding region.

As used herein, the terms "an oligonucleotide having a nucleotide sequence encoding a gene" and "polynucleotide having a nucleotide sequence encoding a gene," means a nucleic acid sequence comprising the coding region of a gene or, in other words, the nucleic acid sequence that encodes a gene product. The coding region may be present in a cDNA, genomic DNA, or RNA form. When present in a DNA form, the oligonucleotide or polynucleotide may be single-stranded (i.e., the sense strand) or double-stranded. Suitable control elements such as enhancers/ promoters, splice junctions, polyadenylation signals, etc. may be placed in close proximity to the coding region of the gene if needed to permit proper initiation of transcription and/or correct processing of the primary RNA transcript. Alternatively, the coding region utilized in the expression vectors of the present invention may contain endogenous enhancers/promoters, splice junctions, intervening sequences, polyadenylation signals, etc. or a combination of both endogenous and exogenous control elements.

As used herein, the term "regulatory element" refers to a genetic element that controls some aspect of the expression of nucleic acid sequences. For example, a promoter is a regulatory element that facilitates the initiation of transcription of an operably linked coding region. Other regulatory elements include splicing signals, polyadenylation signals, termination signals, etc.

As used herein, the terms "complementary" or "complementarity" are used in reference to polynucleotides (i.e., a sequence of nucleotides) related by the base-pairing rules. For example, for the sequence "A-G-T," is complementary to the sequence "T-CA." Complementarity may be "partial," in which only some of the nucleic acids' bases are matched according to the base pairing rules. Or, there may be "complete" or "total" complementarity between the nucleic acids. The degree of complementarity between nucleic acid strands has significant effects on the efficiency and strength of hybridization between nucleic acid strands. This is of particular importance in amplification reactions, as well as detection methods that depend upon binding between nucleic acids.

As used herein, the term "the complement of" a given sequence is used in reference to the sequence that is completely complementary to the sequence over its entire length. For example, the sequence A-G-T-A is "the complement" of the sequence T-C-A-T.

DESCRIPTION OF FIGURES:

The term "homology" refers to a degree of complementarity. There may be partial homology or complete homology (i.e., identity). A partially complementary sequence is one that at least partially inhibits a completely complementary sequence from hybridizing to a target nucleic acid and is referred to using the functional term "substantially homologous." The term "inhibition of binding," when used in reference to nucleic acid binding, refers to inhibition of binding caused by competition of homologous sequences for binding to a target sequence. The inhibition of hybridization of the completely complementary sequence to the target sequence may be examined using a hybridization assay (Southern or Northern blot, solution hybridization and the like) under conditions of low stringency. A substantially homologous sequence or probe will compete for and inhibit the binding (i.e., the hybridization) of a completely homologous sequence to a target under conditions of low stringency. This is not to say that conditions of low stringency are such that non-specific binding is

permitted; low stringency conditions require that the binding of two sequences to one another be a specific (i.e., selective) interaction. The absence of non-specific binding may be tested by the use of a second target that lacks even a partial degree of complementarity (e.g., less than about 30% identity); in the absence of non-specific binding the probe will not hybridize to the second non-complementary target.

The art knows well that numerous equivalent conditions may be employed to comprise low stringency conditions; factors such as the length and nature (DNA, RNA, base composition) of the probe and nature of the target (DNA, RNA, base composition, present in solution or immobilized, etc.) and the concentration of the salts and other components (e.g., the presence or absence of formamide, dextran sulfate, polyethylene glycol) are considered and the hybridization solution may be varied to generate conditions of low stringency hybridization different from, but equivalent to, the above listed conditions. In addition, the art knows conditions that promote hybridization under conditions of high stringency (e.g., increasing the temperature of the hybridization and/or wash steps, the use of formamide in the hybridization solution, etc.).

A gene may produce multiple RNA species that are generated by differential splicing of the primary RNA transcript. cDNAs that are splice variants of the same gene will contain regions of sequence identity or complete homology (representing the presence of the same exon or portion of the same exon on both cDNAs) and regions of complete non-identity (for example, representing the presence of exon "A" on CDNA 1 wherein cDNA 2 contains exon "B" instead). Because the two cDNAs contain regions of sequence identity they will both hybridize to a probe derived from the entire gene or portions of the gene containing sequences found on both cDNAs; the two splice variants are therefore substantially homologous to such a probe and to each other.

When used in reference to a single-stranded nucleic acid sequence, the term "substantially homologous" refers to any probe that can hybridize (i.e., it is the complement of) the single-stranded nucleic acid sequence under conditions of low stringency.

As used herein, the term "competes for binding" is used in reference to a first polypeptide with an activity which binds to the same substrate as does a second polypeptide with an activity, where the second polypeptide is a variant of the first polypeptide or a related or dissimilar polypeptide. The efficiency (e.g., kinetics or thermodynamics) of binding by the first polypeptide may be the same as or greater than or less than the efficiency substrate binding by the second polypeptide. For example, the equilibrium binding constant (KD) for binding to the substrate may be different for the two polypeptides. The term "Km" as used herein refers to the Michaelis-Menton constant for an enzyme and is defined as the concentration of the specific substrate at which a given enzyme yields one-half its maximum velocity in an enzyme catalyzed reaction.

As used herein, the term "hybridization" is used in reference to the pairing of complementary nucleic acids. Hybridization and the strength of hybridization (i.e., the strength of the association between the nucleic acids) is impacted by such factors as the degree of complementary between the nucleic acids, stringency of the conditions involved, the Tm of the formed hybrid, and the G:C ratio within the nucleic acids.

As used herein, the term "Tm" is used in reference to the "melting temperature." The melting temperature is the temperature at which a population of double-stranded nucleic acid molecules becomes half dissociated into single strands. The equation for calculating the Tm of nucleic acids is well known in the art. As indicated by standard references, a simple estimate of the Tm value may be calculated by the equation: Tm=81.5+0.41(% G+C), when a nucleic acid is in aqueous solution at 1 M NaCl (See e.g., Anderson and Young, Quantitative Filter Hybridization, in Nucleic Acid Hybridization (1985)). Other references include more sophisticated computations that take structural as well as sequence characteristics into account for the calculation of Tm, and in some cases the Tm may be determined empirically by beginning with the calculated Tm and testing small increases or decreases of temperature and examining the effect on the population of nucleic acid molecules.

As used herein the term "stringency" is used in reference to the conditions of temperature, ionic strength, and the presence of other compounds such as organic solvents, under which nucleic acid hybridizations are conducted. Those skilled in the art will recognize that "stringency" conditions may be altered by varying the parameters just described either individually or in concert. With "high stringency" conditions, nucleic acid base pairing will occur only between nucleic acid fragments that have a high frequency of complementary base sequences (e.g., hybridization under "high stringency" conditions may occur between homologs with about 85-100% identity, preferably about 70-100% identity). With medium stringency conditions, nucleic acid base pairing will occur between nucleic acids with an intermediate frequency of complementary base sequences (e.g., hybridization under "medium stringency" conditions may occur between homologs with about 50-70% identity). Thus, conditions of "weak" or "low" stringency are often required with nucleic acids that are derived from organisms that are genetically diverse, as the frequency of complementary sequences is usually less.

"High stringency conditions" when used in reference to nucleic acid hybridization comprise conditions equivalent to binding or hybridization at 42 C in a solution consisting of 5X SSPE (43.8 g/l NaCl, 6.9 g/l NaH2PO4 H20 and 1.85 g/l EDTA, pH adjusted to 7.4 with NaOH), 0.5% SDS, 5X Denhardt's reagent and 100 mu g/ml denatured salmon sperm DNA followed by washing in a solution comprising 0.1X SSPE, 1.0% SDS at 42 C when a probe of about 500 nucleotides in length is employed.

"Medium stringency conditions" when used in reference to nucleic acid hybridization comprise conditions equivalent to binding or hybridization at 42 degrees C. in a solution consisting of 5X SSPE (43.8 g/l NaCl, 6.9 g/l NaH2PO4 H20 and 1.85 g/l EDTA, pH adjusted to 7.4 with NaOH), 0.5% SDS, 5X Denhardt's reagent and 100 mu g/ml denatured salmon sperm DNA followed by washing in a solution comprising 1.0X SSPE, 1.0% SDS at 42 C when a probe of about 500 nucleotides in length is employed.

"Low stringency conditions" comprise conditions equivalent to binding or hybridization at 42 C in a solution consisting of 5X SSPE (43.8 g/l NaCl, 6.9 g/l NaH2PO4 H2O and 1.85 g/l EDTA, pH adjusted to 7.4 with NaOH), 0. 1% SDS, 5X Denhardt's reagent (50X Denhardt's contains per 500 ml: 5 g Ficoll (Type 400, Pharamcia), 5 g BSA (Fraction V; Sigma)) and 100 g/ml denatured salmon sperm DNA followed by washing in a solution comprising 5X SSPE, 0.1% SDS at 42 C when a probe of about 500 nucleotides in length is employed.

DESCRIPTION OF FIGURES:

The following terms are used to describe the sequence relationships between two or more polynucleotides: "reference sequence", "sequence identity", and "percentage of sequence identity". A "reference sequence" is a defined sequence used as a basis for a sequence comparison; a reference sequence may be a subset of a larger sequence, for example, as a segment of a full-length cDNA sequence given in a sequence listing or may comprise a complete gene sequence. Generally, a reference sequence is at least 20 nucleotides in length, frequently at least 25 nucleotides in length, and often at least 50 nucleotides in length (e.g. SEQ ID NO:1 may be used as a reference sequence). Since two polynucleotides may each (1) comprise a sequence (i.e., a portion of the complete polynucleotide sequence) that is similar between the two polynucleotides, and (2) may further comprise a sequence that is divergent between the two polynucleotides, sequence comparisons between two (or more) polynucleotides are typically performed by comparing sequences of the two polynucleotides over a "comparison window" to identify and compare local regions of sequence similarity. A "comparison window", as used herein, refers to a conceptual segment of at least 20 contiguous nucleotide positions wherein a polynucleotide sequence may be compared to a reference sequence of at least 20 contiguous nucleotides and wherein the portion of the polynucleotide sequence in the comparison window may comprise additions or deletions (i.e., gaps) of 20 percent or less as compared to the reference sequence (which does not comprise additions or deletions) for optimal alignment of the two sequences. Optimal alignment of sequences for aligning a comparison window may

be conducted by the local homology algorithm of Smith and Waterman (Smith and Waterman, Adv. Appl. Math. 2: 482 (1981)) by the homology alignment algorithm of Needleman and Wunsch (Needleman and Wunsch, J. Mol. Biol. 48:443 (1970)), by the search for similarity method of Pearson and Lipman (Pearson and Lipman, Proc. Natl. Acad. Sci. (U.S.A.) 85:2444 (1988)), by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package Release 7.0, Genetics Computer Group, 575 Science Dr., Madison, Wis.), or by inspection, and the best alignment (i.e., resulting in the highest percentage of homology over the comparison window) generated by the various methods is selected. The term "sequence identity" means that two polynucleotide sequences are identical (i.e., on a nucleotide-by-nucleotide basis) over the window of comparison. The term "percentage of sequence identity" is calculated by comparing two optimally aligned sequences over the window of comparison, determining the number of positions at which the identical nucleic acid base (e.g., A, T, C, G, U, or I) occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison (i.e., the window size), and multiplying the result by 100 to yield the percentage of sequence identity. The window of comparison, as used in the present application, is the entire length of the recited reference sequence (i.e. if SEQ ID NO:1 is recited as the reference sequence, percentage of sequence identity is compared over the entire length of SEQ ID NO:1).

The term "substantial identity" as used herein denotes a characteristic of a polynucleotide sequence, wherein the polynucleotide comprises a sequence that has at least 85 percent sequence identity, preferably at least 90 to 95 percent sequence identity, more usually at least 99 percent sequence identity as compared to a reference sequence over a comparison window of at least 20 nucleotide positions, frequently over a window of at least 25-50 nucleotides (preferably 25-100 nucleotides), wherein the percentage of sequence identity is calculated by comparing the reference sequence to the polynucleotide sequence which may include deletions or additions which total 20 percent or less of the reference sequence over the window of comparison. The reference sequence may be a subset of a larger sequence, for example, as a segment of the full-length sequences of the compositions claimed in the present invention. As applied to polypeptides, the term "substantial identity" means that two peptide sequences, when optimally aligned, such as by the programs GAP or BESTFIT using default gap weights, share at least 80 percent sequence identity, preferably at least 90 percent sequence identity, more preferably at least 95 percent sequence identity or more (e.g., 99 percent sequence identity). Preferably, residue positions that are not identical differ by conservative amino acid substitutions. Conservative amino acid substitutions refer to the interchangeability of residues having similar side chains. For example, a group of amino acids having aliphatic side chains is glycine, alanine, valine, leucine, and isoleucine (e.g., change the valine at position 73 in SEQ ID NO:3 to leucine by changing the G at position 217 of SEQ ID NO:1 to a C); a group of amino acids having aliphatic-hydroxyl side chains is serine and threonine (e.g., change the serine at position 23 in SEQ ID NO:3 to threonine by changing the G at position 68 of SEQ ID NO:1 to a C); a group of amino acids having amide-containing side chains is asparagine and glutamine (e.g., change the glutamine at position 37 of SEQ ID NO:3 to an asparagine by changing the G at position 111 of SEQ ID NO:1 to a C); a group of amino acids having aromatic side chains is phenylalanine, tyrosine, and tryptophan (e.g., change the tyrosine at position 107 in SEQ ID NO:3 to tryptophan by changing the AT at positions 320-21 of SEQ ID NO:1 to GG); a group of amino acids having basic side chains is lysine, arginine, and histidine (e.g., change the histidine at position 35 in SEQ ID NO:3 to arginine by changing the A at position 104 of SEQ ID NO:1 to a G); and a group of amino acids having sulfur-containing side chains is cysteine and methionine (e.g., change the cystein at position 104 in SEQ ID NO:3 to methionine by changing TGT at positions 310-12 of SEQ ID NO:1 to ATG). Preferred conservative amino acids substitution groups are: valine-leucine-isoleucine, phenylalanine-tyrosine, lysinearginine,

alanine-valine, and asparagine-glutamine.

The term "fragment" as used herein refers to a polypeptide that has an amino-terminal and/or carboxy-terminal deletion as compared to the native protein, but where the remaining amino acid sequence is identical to the corresponding positions in the amino acid sequence deduced from a full-length cDNA sequence. Fragments typically are at least 4 amino acids long, preferably at least 20 amino acids long, usually at least 50 amino acids long or longer, and span the portion of the polypeptide required for intermolecular binding of the compositions with its various ligands and/or substrates.

As used herein, the term "genetic variation information" or "genetic variant information" refers to the presence or absence of one or more variant nucleic acid sequences (e.g., polymorphism or mutations) in a given allele of a particular gene (e.g., the human LPH3 gene).

The term "naturally-occurring" as used herein as applied to an object refers to the fact that an object can be found in nature. For example, a polypeptide or polynucleotide sequence that is present in an organism (including viruses) that can be isolated from a source in nature and which has not been intentionally modified by man in the laboratory is naturally-occurring.

"Amplification" is a special case of nucleic acid replication involving template specificity. It is to be contrasted with nonspecific template replication (i.e., replication that is template-dependent but not dependent on a specific template). Template specificity is here distinguished from fidelity of replication (i.e., synthesis of the proper polynucleotide sequence) and nucleotide (ribo- or deoxyribo) specificity. Template specificity is frequently described in terms of "target" specificity. Target sequences are "targets" in the sense that they are sought to be sorted out from other nucleic acid. Amplification techniques have been designed primarily for this sorting out. Template specificity is achieved in most amplification techniques by the choice of enzyme. Amplification enzymes are enzymes that, under conditions they are used, will process only specific sequences of nucleic acid in a heterogeneous mixture of nucleic acid. For example, in the case of Q beta replicase, MDV-1 RNA is the specific template for the replicase (D. L. Kacian et al., Proc. Natl. Acad. Sci. USA 69:3038 (1972)). Other nucleic acids will not be replicated by this amplification enzyme. Similarly, in the case of T7 RNA polymerase, this amplification enzyme has a stringent specificity for its own promoters (Chamberlin et al., Nature 228:227 (1970)). In the case of T4 DNA ligase, the enzyme will not ligate the two oligonucleotides or polynucleotides, where there is a mismatch between the oligonucleotide or polynucleotide substrate and the template at the ligation junction (D. Y. Wu and R. B. Wallace, Genomics 4:560 (1989)). Finally, Taq and Pfu polymerases, by virtue of their ability to function at high temperature, are found to display high specificity for the sequences bounded and thus defined by the primers; the high temperature results in thermodynamic conditions that favor primer hybridization with the target sequences and not hybridization with non-target sequences (H. A. Erlich (ed.), PCR Technology, Stockton Press (1989)).

As used herein, the term "amplifiable nucleic acid" is used in reference to nucleic acids that may be amplified by any amplification method. It is contemplated that "amplifiable nucleic acid" will usually comprise "sample template."

DESCRIPTION OF FIGURES:

As used herein, the term "sample template" refers to nucleic acid originating from a sample that is analyzed for the presence of "target" (defined below). In contrast, "background template" is used in reference to nucleic acid other than sample template that may or may not be present in a sample. Background template is most often inadvertent. It may be the result of carryover, or it may be due to the presence of nucleic acid contaminants sought to be purified away from the sample. For example, nucleic acids from organisms other than those to be ***detected*** may be present as background in a test sample.

As used herein, the term "primer" refers to an oligonucleotide, whether occurring naturally as in a purified restriction digest or produced synthetically, which is capable of acting as a point of initiation of synthesis

when placed under conditions in which synthesis of a primer extension product which is complementary to a nucleic acid strand is induced, (i.e., in the presence of nucleotides and an inducing agent such as DNA polymerase and at a suitable temperature and pH). The primer is preferably single stranded for maximum efficiency in amplification, but may alternatively be double stranded. If double stranded, the primer is first treated to separate its strands before being used to prepare extension products. Preferably, the primer is an oligodeoxyribonucleotide. The primer must be sufficiently long to prime the synthesis of extension products in the presence of the inducing agent. The exact lengths of the primers will depend on many factors, including temperature, source of primer and the use of the method.

As used herein, the term "probe" refers to an oligonucleotide (i. e., a sequence of nucleotides), whether occurring naturally as in a purified restriction digest or produced synthetically, recombinantly or by PCR amplification, that is capable of hybridizing to another oligonucleotide of interest. A probe may be single-stranded or double-stranded. Probes are useful in the detection, identification and isolation of particular gene sequences. It is contemplated that any probe used in the present invention may be labeled with any "reporter molecule," so that is detectable in any ***detection*** system, including, but not limited to enzyme (e.g., ELISA, as well as enzyme-based histochemical assays), ***fluorescent*** , radioactive, and luminescent systems. It is not intended that the present invention be limited to any particular ***detection*** system or label.

As used herein, the term "target," refers to a nucleic acid sequence or structure to be detected or characterized. Thus, the "target" is sought to be sorted out from other nucleic acid sequences. A "segment" is defined as a region of nucleic acid within the target sequence.

As used herein, the term "polymerase chain reaction" ("PCR") refers to the method described by Kleppe, et al., J. Molecular Biology, 56, 1971, pp. 341-361, and in U.S. Pat. Nos. 4,683,195, 4,683,202, and 4,965,188, hereby incorporated by reference, that describe a method for increasing the concentration of a segment of a target sequence in a mixture of genomic DNA without cloning or purification. This process for amplifying the target sequence consists of introducing a large excess of two oligonucleotide primers to the DNA mixture containing the desired target sequence, followed by a precise sequence of thermal cycling in the presence of a DNA polymerase. The two primers are complementary to their respective strands of the double stranded target sequence. To effect amplification, the mixture is denatured and the primers then annealed to their complementary sequences within the target molecule. Following annealing, the primers are extended with a polymerase so as to form a new pair of complementary strands. The steps of denaturation, primer annealing, and polymerase extension can be repeated many times (i.e., denaturation, annealing and extension constitute one "cycle"; there can be numerous "cycles") to obtain a high concentration of an amplified segment of the desired target sequence. The length of the amplified segment of the desired target sequence is determined by the relative positions of the primers with respect to each other, and therefore, this length is a controllable parameter. By virtue of the repeating aspect of the process, the method is referred to as the "polymerase chain reaction" (hereinafter "PCR"). Because the desired amplified segments of the target sequence become the predominant sequences (in terms of concentration) in the mixture, they are said to be "PCR amplified." With PCR, it is possible to amplify a single copy of a specific target sequence in genomic DNA to a level detectable by several different methodologies (e.g., hybridization with a labeled probe; incorporation of biotinylated primers followed by avidinenzyme conjugate detection; incorporation of 32P-labeled deoxynucleotide triphosphates, such as dCTP or dATP, into the amplified segment). In addition to genomic DNA, any oligonucleotide or polynucleotide sequence can be amplified with the appropriate set of primer molecules. In particular, the amplified segments created by the PCR process itself are, themselves, efficient templates for subsequent PCR amplifications.

As used herein, the terms "PCR product," "PCR fragment," and "amplification product" refer to the resultant mixture of compounds after two or more cycles of the PCR steps of denaturation, annealing and extension are complete. These terms encompass the case where there has been amplification of one or more segments of one or more target sequences.

As used herein, the term "amplification reagents" refers to those reagents (deoxyribonucleotide triphosphates, buffer, etc.) , needed for amplification except for primers, nucleic acid template, and the amplification enzyme . Typically, amplification reagents along with other reaction components are placed and contained in a reaction vessel (test tube, microwell, etc.).

As used herein, the terms "restriction endonucleases" and "restriction ***enzymes*** " refer to bacterial enzymes, each of which cut double-stranded DNA at or near a specific nucleotide sequence.

As used herein, the term "antisense" is used in reference to RNA sequences that are complementary to a specific RNA sequence (e. g., MRNA). Antisense RNA may be produced by any method, including synthesis by splicing the gene(s) of interest in a reverse orientation to a viral promoter that permits the synthesis of a coding strand. Once introduced into an embryo, this transcribed strand combines with natural mRNA produced by the embryo to form duplexes. These duplexes then block either the further transcription of the mRNA or its translation. In this manner, mutant phenotypes may be generated. The term "antisense strand" is used in reference to a nucleic acid strand that is complementary to the "sense" strand. The designation (-) (i.e., "negative") is sometimes used in reference to the antisense strand, with the designation (+) sometimes used in reference to the sense (i.e., "positive") strand.

The term "isolated" when used in relation to a nucleic acid, as in "an isolated oligonucleotide" or "isolated polynucleotide" refers to a nucleic acid sequence that is identified and separated from at least one contaminant nucleic acid with which it is ordinarily associated in its natural source. Isolated nucleic acid is present in a form or setting that is different from that in which it is found in nature. In contrast, nonisolated nucleic acids are nucleic acids such as DNA and RNA found in the state they exist in nature. For example, a given DNA sequence (e.g., a gene) is found on the host cell chromosome in proximity to neighboring genes; RNA sequences, such as a specific mRNA sequence encoding a specific protein, are found in the cell as a mixture with numerous other mRNAs that encode a multitude of proteins. However, isolated nucleic acid encoding LPH3 includes, by way of example, such nucleic acid in cells ordinarily expressing LPH3 (e.g. trabecular meshwork cells) where the nucleic acid is in a chromosomal location different from that of natural cells, or is otherwise flanked by a different nucleic acid sequence than that found in nature. The isolated nucleic acid, oligonucleotide, or polynucleotide may be present in single-stranded or doublestranded form. When an isolated nucleic acid, oligonucleotide or polynucleotide is to be utilized to express a protein, the oligonucleotide or polynucleotide will contain at a minimum the sense or coding strand (i. e., the oligonucleotide or polynucleotide may single-stranded), but may contain both the sense and anti-sense strands (i.e., the oligonucleotide or polynucleotide may be double-stranded).

As used herein the term "portion" when in reference to a nucleotide sequence (as in "a portion of a given nucleotide sequence") refers to fragments of that sequence. The fragments may range in size from four nucleotides to the entire nucleotide sequence minus one nucleotide (10 nucleotides, 20, 30, 40, 50, 100, 200, etc.).

As used herein the term "coding region" when used in reference to structural gene refers to the nucleotide sequences that encode the amino acids found in the nascent polypeptide as a result of translation of a MRNA molecule. The coding region is bounded, in eukaryotes, on the 5' side by the nucleotide triplet "ATG" that encodes the initiator methionine and on the 3' side by one of the three triplets, which specify stop codons (i.e., TAA, TAG, TGA).

DESCRIPTION OF FIGURES:

As used herein, the term "purified" or "to purify" refers to the removal of contaminants from a sample. For example, LPH3 antibodies are purified by

removal of contaminating nonimmunoglobulin proteins; they are also purified by the removal of immunoglobulin that does not bind LPH3. The removal of nonimmunoglobulin proteins and/or the removal of immunoglobulins that do not bind LPH3 results in an increase in the percent of LPH3-reactive immunoglobulins in the sample. In another example, recombinant LPH3 polypeptides are expressed in bacterial host cells and the polypeptides are purified by the removal of host cell proteins; the percent of recombinant LPH3 polypeptides is thereby increased in the sample.

The term "recombinant DNA molecule" as used herein refers to a DNA molecule that is comprised of segments of DNA joined together by means of molecular biological techniques.

The term "recombinant protein" or "recombinant polypeptide" as used herein refers to a protein molecule that is expressed from a recombinant DNA molecule.

The term "native protein" as used herein to indicate that a protein does not contain amino acid residues encoded by vector sequences; that is the native protein contains only those amino acids found in the protein as it occurs in nature. A native protein may be produced by recombinant means or may be isolated from a naturally occurring source.

The term "Southern blot," refers to the analysis of DNA on agarose or acrylamide gels to fractionate the DNA according to size followed by transfer of the DNA from the gel to a solid support, such as nitrocellulose or a nylon membrane. The immobilized DNA is then probed with a labeled probe to detect DNA species complementary to the probe used. The DNA may be cleaved with restriction enzymes prior to electrophoresis. Following electrophoresis, the DNA may be partially depurinated and denatured prior to or during transfer to the solid support. Southern blots are a standard tool of molecular biologists (J. Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, NY, pp 9.31-9.58 (1989)).

The term "Northern blot," as used herein refers to the analysis of RNA by electrophoresis of RNA on agarose gels to fractionate the RNA according to size followed by transfer of the RNA from the gel to a solid support, such as nitrocellulose or a nylon membrane. The immobilized RNA is then probed with a labeled probe to detect RNA species complementary to the probe used. Northern blots are a standard tool of molecular biologists (J. Sambrook, et al, supra, pp 7.39-7.52 (1989)).

The term "Western blot" refers to the analysis of protein(s) (or polypeptides) immobilized onto a support such as nitrocellulose or a membrane. The proteins are run on acrylamide gels to separate the proteins, followed by transfer of the protein from the gel to a solid support, such as nitrocellulose or a nylon membrane. The immobilized proteins are then exposed to antibodies with reactivity against an antigen of interest. The binding of the antibodies may be detected by various methods, including the use of radiolabelled antibodies.

The term "antigenic determinant" as used herein refers to that portion of an antigen that makes contact with a particular antibody (i.e., an epitope). When a protein or fragment of a protein is used to immunize a host animal, numerous regions of the protein may induce the production of antibodies that bind specifically to a given region or three-dimensional structure on the protein; these regions or structures are referred to as antigenic determinants. An antigenic determinant may compete with the intact antigen (i.e., the "immunogen" used to elicit the immune response) for binding to an antibody.

The term "transgene" as used herein refers to a foreign, heterologous, or autologous gene that is placed into an organism by introducing the gene into newly fertilized eggs or early embryos. The term "foreign gene" refers to any nucleic acid (e.g., gene sequence) that is introduced into the genome of an animal by experimental manipulations and may include gene sequences found in that animal so long as the introduced gene does not reside in the same location as does the naturallyoccurring gene. The term "autologous gene" is intended to encompass variants (e.g., polymorphisms or mutants) of the naturally occurring gene. The term transgene thus encompasses the replacement of the naturally occurring gene with a variant form of the gene.

As used herein, the term "vector" is used in reference to nucleic acid

molecules that transfer DNA segment(s) from one cell to another. The term "vehicle" is sometimes used interchangeably with "vector."

The term "expression vector" as used herein refers to a recombinant DNA molecule containing a desired coding sequence and appropriate nucleic acid sequences necessary for the expression of the operably linked coding sequence in a particular host organism. Nucleic acid sequences necessary for expression in prokaryotes usually include a promoter, an operator (optional), and a ribosome binding site, often along with other sequences. Eukaryotic cells are known to utilize promoters, enhancers, and termination and polyadenylation signals.

As used herein, the term "host cell" refers to any eukaryotic or prokaryotic cell (e.g., bacterial cells such as E. coli, yeast cells, mammalian cells, avian cells, amphibian cells, plant cells, fish cells, and insect cells), whether located in vitro or in vivo. For example, host cells may be located in a transgenic animal.

The terms "overexpression" and "overexpressing" and grammatical equivalents, are used in reference to levels of mRNA to indicate a level of expression approximately 3-fold higher than that typically observed in a given tissue in a control or nontransgenic animal. Levels of mRNA are measured using any of a number of techniques known to those skilled in the art including, but not limited to Northern blot analysis (See, Example 10, for a protocol for performing Northern blot analysis). Appropriate controls are included on the Northern blot to control for differences in the amount of RNA loaded from each tissue analyzed (e.g., the amount of 28S rRNA, an abundant RNA transcript present at essentially the same amount in all tissues, present in each sample can be used as a means of normalizing or standardizing the RAD50 mRNA-specific signal observed on Northern blots). The amount of MRNA present in the band corresponding in size to the correctly spliced LPH (e.g. human LPH3) transgene RNA is quantified; other minor species of RNA which hybridize to the transgene probe are not considered in the quantification of the expression of the transgenic mRNA.

The term "transfection" as used herein refers to the introduction of foreign DNA into eukaryotic cells. Transfection may be accomplished by a variety of means known to the art including calcium phosphate-DNA co-precipitation, DEAE-dextranmediated transfection, polybrene-mediated transfection, electroporation, microinjection, liposome fusion, lipofection, protoplast fusion, retroviral infection, and biolistics.

The term "stable transfection" or "stably transfected" refers to the introduction and integration of foreign DNA into the genome of the transfected cell. The term "stable transfectant" refers to a cell that has stably integrated foreign DNA into the genomic DNA.

The term "transient transfection" or "transiently transfected" refers to the introduction of foreign DNA into a cell where the foreign DNA fails to integrate into the genome of the transfected cell. The foreign DNA persists in the nucleus of the transfected cell for several days. During this time the foreign DNA is subject to the regulatory controls that govern the expression of endogenous genes in the chromosomes. The term "transient transfectant" refers to cells that have taken up foreign DNA but have failed to integrate this DNA.

The term "calcium phosphate co-precipitation" refers to a technique for the introduction of nucleic acids into a cell. The uptake of nucleic acids by cells is enhanced when the nucleic acid is presented as a calcium phosphate-nucleic acid co-precipitate. The original technique of Graham and van der Eb (Graham and van der Eb, Virol., 52:456 (1973)), has been modified by several groups to optimize conditions for particular types of cells. The art is well aware of these numerous modifications.

A "composition comprising a given polynucleotide sequence" as used herein refers broadly to any composition containing the given polynucleotide sequence. The composition may comprise an aqueous solution. Compositions comprising polynucleotide sequences encoding LPH3 (e.g., SEQ ID NO:1) or fragments thereof may be employed as hybridization probes. In this case, the LPH3 encoding polynucleotide sequences are typically employed in an aqueous solution

containing salts (e.g., NaCl), detergents (e.g., SDS), and other components (e.g., Denhardt's solution, dry milk, salmon sperm DNA, etc.).
The term "test compound" or "candidate compound" refer to any chemical entity, pharmaceutical, drug, and the like that can be used to treat or prevent a disease, illness, sickness, or disorder of bodily function, or otherwise alter the physiological or cellular status of a sample. Test compounds comprise both known and potential therapeutic compounds. A test compound can be determined to be therapeutic by screening using the screening methods of the present invention. A "known therapeutic compound" refers to a therapeutic compound that has been shown (e.g., through animal trials or prior experience with administration to humans) to be effective in such treatment or prevention.
As used herein, the term "response," when used in reference to an assay, refers to the generation of a detectable signal (e.g., accumulation of reporter protein, increase in ion concentration, accumulation of a detectable chemical product).

DESCRIPTION OF FIGURES:

As used herein, the term "reporter gene" refers to a gene encoding a protein that may be assayed. Examples of reporter genes include, but are not limited to, luciferase (See, e.g., deWet et al., Mol. Cell. Biol. 7:725 (1987) and U.S. Pat Nos., 6,074,859, incorporated herein by reference), green fluorescent protein (e.g., GenBank Accession Number U43284; a number of GFP variants are commercially available from CLONTECH Laboratories, Palo Alto, Calif.), chloramphenicol acetyltransferase, betagalactosidase, alkaline phosphatase, and horse radish peroxidase.
As used herein, the terms "computer memory" and "computer memory device" refer to any storage media readable by a computer processor. Examples of computer memory include, but are not limited to, RAM, ROM, computer chips, digital video disc (DVDs), compact discs (CDs), hard disk drives (HDD), and magnetic tape.
As used herein, the term "computer readable medium" refers to any device or system for storing and providing information (e.g. , data and instructions) to a computer processor. Examples of computer readable media include, but are not limited to, DVDs, CDs, hard disk drives, magnetic tape and servers for streaming media over networks.
As used herein, the phrase "computer readable medium encodes a representation" of a nucleic acid or amino acid sequence, refers to computer readable medium that has stored thereon information, that when delivered to a processor, allows the sequence of the nucleic or amino acid sequence to be displayed to a user (e.g. printed out or presented on a display screen).
As used herein, the terms "processor" and "central processing unit" or "CPU" are used interchangeably and refer to a device that is able to read a program from a computer memory (e.g., ROM or other computer memory) and perform a set of steps according to the program. !

AB The present invention relates to Latrophilin (LPH) polynucleotides and polypeptides, and to identifying and treating subjects at risk for eye disease. Specifically, the present invention provides novel human LPH3 and LPH1 polynucleotides and LPH3 polypeptides, assays for detecting variations in LPH polynucleotides associated with eye disease, and methods and compositions for treating eye disease.

CLMN 23 82 Figure(s).

FIG. 1 shows the cDNA nucleic acid sequence of human LPH3 (SEQ ID NO:1).
FIG. 2 shows the cDNA nucleic acid sequence of human LPH3 with additional 5' and 3' flanking regions (SEQ ID NO:2).
FIG. 3 shows a sequence alignment between the cDNA sequence of human LPH3 (SEQ ID NO:1), and accession Nos. AF307080 (human LEC3) and AB018311.
FIG. 4 shows both the nucleotide (SEQ ID NO:1) and peptide (SEQ ID NO:3) sequences of human LPH3.
FIG. 5 shows the amino acid sequence of human LPH3 (SEQ ID NO:3) and the amino acid sequence of human LEC3 (SEQ ID NO:4, accession no. AF307080).
FIG. 6 shows the exon regions of human genomic LPH3 shown in SEQ ID NO:5.
FIG. 7 shows the human genomic sequence of human LPH3 (SEQ ID NO:5), with the intronic/non-coding regions in lower case, and the exon regions shown

in uppercase and bold.

FIG. 8 shows the exon regions of human genomic LPH1 shown in SEQ ID NO:32.

FIG. 9 shows the human genomic sequence of human LPH1 (SEQ ID NO:32), with the intronic/non-coding regions in lower case, and the exon regions shown in uppercase and bold.

FIG. 10 shows a hypothetical model of LPH-TIGR interaction. Importantly, the present invention is not limited to a particular mechanism of action. Indeed, an understanding of the mechanism of action is not necessary to practice the present invention. Nevertheless, this figure depicts a hypothetical model of LPH-TIGR interaction.

FIG. 11 shows the cDNA sequence of human TIGR/myocilin (SEQ ID NO:172, accession no. NM-000261), and the amino acid sequence of human TIGR/myocilin (SEQ ID NO:173, accession no. NP-000252. Nucleotides 758-1528 of SEQ ID NO:172 encode an olfactomedin domain, and amino acids 246-502 of SEQ ID NO:173 represent an olfactomedin domain of the human TIGR peptide.

Definitions

To facilitate an understanding of the invention, a number of terms are defined below.

As used herein, the terms "subject" and "patient" refer to any animal, such as a mammal like a dog, cat, bird, livestock, and preferably a human. Specific examples of "subjects" and "patients" include, but are not limited to, individuals with glaucoma, individuals with glaucoma-related characteristics such as ocular hypertension, relatives of such individuals, and individuals at risk of glaucoma (e.g. individuals with a family history of glaucoma, and individuals over the age of 40).

As used herein, the term "eye disease" refers to diseases affecting all, or a portion of the eye, including, but not limited to, Primary Open-Angle Glaucoma (e.g. juvenile onset and adult onset), occular hypertension, and other eye diseases where, for example, the intraocular pressure is elevated.

The term "LPH gene" refers to a full-length LPH nucleotide sequence (e.g., SEQ ID NO:5 for LPH3, and SEQ ID NO:32 for LPH1) . However, it is also intended that the term encompass fragments of the genomic LPH sequences, the cDNA sequences (e.g. SEQ ID NO:1) as well as other domains within the full-length LPH nucleotide sequences. Furthermore, the terms "LPH nucleotide sequence" or "LPH polynucleotide sequence" encompasses DNA, cDNA, and RNA (e.g., MRNA) sequences.

In addition to containing introns, genomic forms of a gene may also include sequences located on both the 5' and 3' end of the sequences that are present on the RNA transcript. These sequences are referred to as "flanking" sequences or regions (these flanking sequences are located 5' or 3' to the nontranslated sequences present on the mRNA transcript). The 5' flanking region may contain regulatory sequences such as promoters and enhancers that control or influence the transcription of the gene. The 3' flanking region may contain sequences that direct the termination of transcription, posttranscriptional cleavage and polyadenylation.

Where "amino acid sequence" is recited herein to refer to an amino acid sequence of a naturally occurring protein molecule, "amino acid sequence" and like terms, such as "polypeptide" or "protein" are not meant to limit the amino acid sequence to the complete, native amino acid sequence associated with the recited protein molecule.

The term "wild-type" refers to a gene or gene product that has the characteristics of that gene or gene product when isolated from a naturally occurring source. A wild-type gene is that which is most frequently observed in a population and is thus arbitrarily designed the "normal" or "wild-type" form of the gene. In contrast, the term "variant" refers to a gene or gene product that displays modifications in sequence and/or functional properties (i.e., altered characteristics) when compared to the wild-type gene or gene product. Examples of variants

include, but are not limted to, polymorphisms and mutations. It is noted that naturally-occurring mutants can be isolated; these are identified by the fact that they have altered characteristics when compared to the wild-type gene or gene product.

As used herein, the terms "nucleic acid molecule encoding," "DNA sequence encoding," and "DNA encoding" refer to the order or sequence of deoxyribonucleotides along a strand of deoxyribonucleic acid. The order of these deoxyribonucleotides determines the order of amino acids along the polypeptide (protein) chain. The DNA sequence thus codes for the amino acid sequence.

DNA molecules are said to have "5' ends" and "3' ends" because mononucleotides are reacted to make oligonucleotides or polynucleotides in a manner such that the 5' phosphate of one mononucleotide pentose ring is attached to the 3' oxygen of its neighbor in one direction via a phosphodiester linkage. Therefore, an end of an oligonucleotides or polynucleotide, referred to as the "5' end" if its 5' phosphate is not linked to the 3' oxygen of a mononucleotide pentose ring and as the "3' end" if its 3' oxygen is not linked to a 5' phosphate of a subsequent mononucleotide pentose ring. As used herein, a nucleic acid sequence, even if internal to a larger oligonucleotide or polynucleotide, also may be said to have 5' and 3' ends. In either a linear or circular DNA molecule, discrete elements are referred to as being "upstream" or 5' of the "downstream" or 3' elements. This terminology reflects the fact that transcription proceeds in a 5' to 3' fashion along the DNA strand. The promoter and enhancer elements that direct transcription of a linked gene are generally located 5' or upstream of the coding region. However, enhancer elements can exert their effect even when located 3' of the promoter element and the coding region. Transcription termination and polyadenylation signals are located 3' or downstream of the coding region.

As used herein, the terms "an oligonucleotide having a nucleotide sequence encoding a gene" and "polynucleotide having a nucleotide sequence encoding a gene," means a nucleic acid sequence comprising the coding region of a gene or, in other words, the nucleic acid sequence that encodes a gene product. The coding region may be present in a cDNA, genomic DNA, or RNA form. When present in a DNA form, the oligonucleotide or polynucleotide may be single-stranded (i.e., the sense strand) or double-stranded. Suitable control elements such as enhancers/ promoters, splice junctions, polyadenylation signals, etc. may be placed in close proximity to the coding region of the gene if needed to permit proper initiation of transcription and/or correct processing of the primary RNA transcript. Alternatively, the coding region utilized in the expression vectors of the present invention may contain endogenous enhancers/promoters, splice junctions, intervening sequences, polyadenylation signals, etc. or a combination of both endogenous and exogenous control elements.

As used herein, the term "regulatory element" refers to a genetic element that controls some aspect of the expression of nucleic acid sequences. For example, a promoter is a regulatory element that facilitates the initiation of transcription of an operably linked coding region. Other regulatory elements include splicing signals, polyadenylation signals, termination signals, etc.

As used herein, the terms "complementary" or "complementarity" are used in reference to polynucleotides (i.e., a sequence of nucleotides) related by the base-pairing rules. For example, for the sequence "A-G-T," is complementary to the sequence "T-CA." Complementarity may be "partial," in which only some of the nucleic acids' bases are matched according to the base pairing rules. Or, there may be "complete" or "total" complementarity between the nucleic acids. The degree of complementarity between nucleic acid strands has significant effects on the efficiency and strength of hybridization between nucleic acid strands. This is of

particular importance in amplification reactions, as well as detection methods that depend upon binding between nucleic acids.

As used herein, the term "the complement of" a given sequence is used in reference to the sequence that is completely complementary to the sequence over its entire length. For example, the sequence A-G-T-A is "the complement" of the sequence T-C-A-T.

The term "homology" refers to a degree of complementarity. There may be partial homology or complete homology (i.e., identity). A partially complementary sequence is one that at least partially inhibits a completely complementary sequence from hybridizing to a target nucleic acid and is referred to using the functional term "substantially homologous." The term "inhibition of binding," when used in reference to nucleic acid binding, refers to inhibition of binding caused by competition of homologous sequences for binding to a target sequence. The inhibition of hybridization of the completely complementary sequence to the target sequence may be examined using a hybridization assay (Southern or Northern blot, solution hybridization and the like) under conditions of low stringency. A substantially homologous sequence or probe will compete for and inhibit the binding (i.e., the hybridization) of a completely homologous sequence to a target under conditions of low stringency. This is not to say that conditions of low stringency are such that non-specific binding is permitted; low stringency conditions require that the binding of two sequences to one another be a specific (i.e., selective) interaction. The absence of non-specific binding may be tested by the use of a second target that lacks even a partial degree of complementarity (e.g., less than about 30% identity); in the absence of non-specific binding the probe will not hybridize to the second non-complementary target.

The art knows well that numerous equivalent conditions may be employed to comprise low stringency conditions; factors such as the length and nature (DNA, RNA, base composition) of the probe and nature of the target (DNA, RNA, base composition, present in solution or immobilized, etc.) and the concentration of the salts and other components (e.g., the presence or absence of formamide, dextran sulfate, polyethylene glycol) are considered and the hybridization solution may be varied to generate conditions of low stringency hybridization different from, but equivalent to, the above listed conditions. In addition, the art knows conditions that promote hybridization under conditions of high stringency (e.g., increasing the temperature of the hybridization and/or wash steps, the use of formamide in the hybridization solution, etc.).

A gene may produce multiple RNA species that are generated by differential splicing of the primary RNA transcript. cDNAs that are splice variants of the same gene will contain regions of sequence identity or complete homology (representing the presence of the same exon or portion of the same exon on both cDNAs) and regions of complete non-identity (for example, representing the presence of exon "A" on CDNA 1 wherein cDNA 2 contains exon "B" instead). Because the two cDNAs contain regions of sequence identity they will both hybridize to a probe derived from the entire gene or portions of the gene containing sequences found on both cDNAs; the two splice variants are therefore substantially homologous to such a probe and to each other.

When used in reference to a single-stranded nucleic acid sequence, the term "substantially homologous" refers to any probe that can hybridize (i.e., it is the complement of) the single-stranded nucleic acid sequence under conditions of low stringency.

As used herein, the term "competes for binding" is used in reference to a first polypeptide with an activity which binds to the same substrate as does a second polypeptide with an activity, where the second polypeptide is a variant of the first polypeptide or a related or dissimilar polypeptide. The efficiency (e.g., kinetics or thermodynamics) of binding by the first polypeptide may be the same as or greater than or less than

the efficiency substrate binding by the second polypeptide. For example, the equilibrium binding constant (KD) for binding to the substrate may be different for the two polypeptides. The term "Km" as used herein refers to the Michaelis-Menton constant for an enzyme and is defined as the concentration of the specific substrate at which a given enzyme yields one-half its maximum velocity in an enzyme catalyzed reaction.

As used herein, the term "hybridization" is used in reference to the pairing of complementary nucleic acids. Hybridization and the strength of hybridization (i.e., the strength of the association between the nucleic acids) is impacted by such factors as the degree of complementary between the nucleic acids, stringency of the conditions involved, the Tm of the formed hybrid, and the G:C ratio within the nucleic acids.

As used herein, the term "Tm" is used in reference to the "melting temperature." The melting temperature is the temperature at which a population of double-stranded nucleic acid molecules becomes half dissociated into single strands. The equation for calculating the Tm of nucleic acids is well known in the art. As indicated by standard references, a simple estimate of the Tm value may be calculated by the equation: Tm=81.5+0.41(% G+C), when a nucleic acid is in aqueous solution at 1 M NaCl (See e.g., Anderson and Young, Quantitative Filter Hybridization, in Nucleic Acid Hybridization (1985)). Other references include more sophisticated computations that take structural as well as sequence characteristics into account for the calculation of Tm, and in some cases the Tm may be determined empirically by beginning with the calculated Tm and testing small increases or decreases of temperature and examining the effect on the population of nucleic acid molecules.

As used herein the term "stringency" is used in reference to the conditions of temperature, ionic strength, and the presence of other compounds such as organic solvents, under which nucleic acid hybridizations are conducted. Those skilled in the art will recognize that "stringency" conditions may be altered by varying the parameters just described either individually or in concert. With "high stringency" conditions, nucleic acid base pairing will occur only between nucleic acid fragments that have a high frequency of complementary base sequences (e.g., hybridization under "high stringency" conditions may occur between homologs with about 85-100% identity, preferably about 70-100% identity). With medium stringency conditions, nucleic acid base pairing will occur between nucleic acids with an intermediate frequency of complementary base sequences (e.g., hybridization under "medium stringency" conditions may occur between homologs with about 50-70% identity). Thus, conditions of "weak" or "low" stringency are often required with nucleic acids that are derived from organisms that are genetically diverse, as the frequency of complementary sequences is usually less.

"High stringency conditions" when used in reference to nucleic acid hybridization comprise conditions equivalent to binding or hybridization at 42 C in a solution consisting of 5X SSPE (43.8 g/l NaCl, 6.9 g/l NaH2PO4 H20 and 1.85 g/l EDTA, pH adjusted to 7.4 with NaOH), 0.5% SDS, 5X Denhardt's reagent and 100 mu g/ml denatured salmon sperm DNA followed by washing in a solution comprising 0.1X SSPE, 1.0% SDS at 42 C when a probe of about 500 nucleotides in length is employed.

"Medium stringency conditions" when used in reference to nucleic acid hybridization comprise conditions equivalent to binding or hybridization at 42 degrees C. in a solution consisting of 5X SSPE (43.8 g/l NaCl, 6.9 g/l NaH2PO4 H20 and 1.85 g/l EDTA, pH adjusted to 7.4 with NaOH), 0.5% SDS, 5X Denhardt's reagent and 100 mu g/ml denatured salmon sperm DNA followed by washing in a solution comprising 1.0X SSPE, 1.0% SDS at 42 C when a probe of about 500 nucleotides in length is employed.

"Low stringency conditions" comprise conditions equivalent to binding or hybridization at 42 C in a solution consisting of 5X SSPE (43.8 g/l NaCl, 6.9 g/l NaH2PO4 H2O and 1.85 g/l EDTA, pH adjusted to 7.4 with NaOH), 0.1% SDS, 5X Denhardt's reagent (50X Denhardt's contains per 500 ml: 5 g

Ficoll (Type 400, Pharamcia), 5 g BSA (Fraction V; Sigma)) and 100 g/ml denatured salmon sperm DNA followed by washing in a solution comprising 5X SSPE, 0.1% SDS at 42 C when a probe of about 500 nucleotides in length is employed.

The following terms are used to describe the sequence relationships between two or more polynucleotides: "reference sequence", "sequence identity", and "percentage of sequence identity". A "reference sequence" is a defined sequence used as a basis for a sequence comparison; a reference sequence may be a subset of a larger sequence, for example, as a segment of a full-length cDNA sequence given in a sequence listing or may comprise a complete gene sequence. Generally, a reference sequence is at least 20 nucleotides in length, frequently at least 25 nucleotides in length, and often at least 50 nucleotides in length (e.g. SEQ ID NO:1 may be used as a reference sequence). Since two polynucleotides may each (1) comprise a sequence (i.e., a portion of the complete polynucleotide sequence) that is similar between the two polynucleotides, and (2) may further comprise a sequence that is divergent between the two polynucleotides, sequence comparisons between two (or more) polynucleotides are typically performed by comparing sequences of the two polynucleotides over a "comparison window" to identify and compare local regions of sequence similarity. A "comparison window", as used herein, refers to a conceptual segment of at least 20 contiguous nucleotide positions wherein a polynucleotide sequence may be compared to a reference sequence of at least 20 contiguous nucleotides and wherein the portion of the polynucleotide sequence in the comparison window may comprise additions or deletions (i.e., gaps) of 20 percent or less as compared to the reference sequence (which does not comprise additions or deletions) for optimal alignment of the two sequences. Optimal alignment of sequences for aligning a comparison window may be conducted by the local homology algorithm of Smith and Waterman (Smith and Waterman, Adv. Appl. Math. 2: 482 (1981)) by the homology alignment algorithm of Needleman and Wunsch (Needleman and Wunsch, J. Mol. Biol. 48:443 (1970)), by the search for similarity method of Pearson and Lipman (Pearson and Lipman, Proc. Natl. Acad. Sci. (U.S.A.) 85:2444 (1988)), by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package Release 7.0, Genetics Computer Group, 575 Science Dr., Madison, Wis.), or by inspection, and the best alignment (i.e., resulting in the highest percentage of homology over the comparison window) generated by the various methods is selected. The term "sequence identity" means that two polynucleotide sequences are identical (i.e., on a nucleotide-by-nucleotide basis) over the window of comparison. The term "percentage of sequence identity" is calculated by comparing two optimally aligned sequences over the window of comparison, determining the number of positions at which the identical nucleic acid base (e.g., A, T, C, G, U, or I) occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison (i.e., the window size), and multiplying the result by 100 to yield the percentage of sequence identity. The window of comparison, as used in the present application, is the entire length of the recited reference sequence (i.e. if SEQ ID NO:1 is recited as the reference sequence, percentage of sequence identity is compared over the entire length of SEQ ID NO:1).

The term "substantial identity" as used herein denotes a characteristic of a polynucleotide sequence, wherein the polynucleotide comprises a sequence that has at least 85 percent sequence identity, preferably at least 90 to 95 percent sequence identity, more usually at least 99 percent sequence identity as compared to a reference sequence over a comparison window of at least 20 nucleotide positions, frequently over a window of at least 25-50 nucleotides (preferably 25-100 nucleotides), wherein the percentage of sequence identity is calculated by comparing the reference sequence to the polynucleotide sequence which may include

deletions or additions which total 20 percent or less of the reference sequence over the window of comparison. The reference sequence may be a subset of a larger sequence, for example, as a segment of the full-length sequences of the compositions claimed in the present invention. As applied to polypeptides, the term "substantial identity" means that two peptide sequences, when optimally aligned, such as by the programs GAP or BESTFIT using default gap weights, share at least 80 percent sequence identity, preferably at least 90 percent sequence identity, more preferably at least 95 percent sequence identity or more (e.g., 99 percent sequence identity). Preferably, residue positions that are not identical differ by conservative amino acid substitutions. Conservative amino acid substitutions refer to the interchangeability of residues having similar side chains. For example, a group of amino acids having aliphatic side chains is glycine, alanine, valine, leucine, and isoleucine (e.g., change the valine at position 73 in SEQ ID NO:3 to leucine by changing the G at position 217 of SEQ ID NO:1 to a C); a group of amino acids having aliphatic-hydroxyl side chains is serine and threonine (e.g., change the serine at position 23 in SEQ ID NO:3 to threonine by changing the G at position 68 of SEQ ID NO:1 to a C); a group of amino acids having amide-containing side chains is asparagine and glutamine (e.g., change the glutamine at position 37 of SEQ ID NO:3 to an asparagine by changing the G at position 111 of SEQ ID NO:1 to a C); a group of amino acids having aromatic side chains is phenylalanine, tyrosine, and tryptophan (e.g., change the tyrosine at position 107 in SEQ ID NO:3 to tryptophan by changing the AT at positions 320-21 of SEQ ID NO:1 to GG); a group of amino acids having basic side chains is lysine, arginine, and histidine (e.g., change the histidine at position 35 in SEQ ID NO:3 to arginine by changing the A at position 104 of SEQ ID NO:1 to a G); and a group of amino acids having sulfur-containing side chains is cysteine and methionine (e.g., change the cystein at position 104 in SEQ ID NO:3 to methionine by changing TGT at positions 310-12 of SEQ ID NO:1 to ATG). Preferred conservative amino acids substitution groups are: valine-leucine-isoleucine, phenylalanine-tyrosine, lysinearginine, alanine-valine, and asparagine-glutamine.

The term "fragment" as used herein refers to a polypeptide that has an amino-terminal and/or carboxy-terminal deletion as compared to the native protein, but where the remaining amino acid sequence is identical to the corresponding positions in the amino acid sequence deduced from a full-length cDNA sequence. Fragments typically are at least 4 amino acids long, preferably at least 20 amino acids long, usually at least 50 amino acids long or longer, and span the portion of the polypeptide required for intermolecular binding of the compositions with its various ligands and/or substrates.

As used herein, the term "genetic variation information" or "genetic variant information" refers to the presence or absence of one or more variant nucleic acid sequences (e.g., polymorphism or mutations) in a given allele of a particular gene (e.g., the human LPH3 gene).

The term "naturally-occurring" as used herein as applied to an object refers to the fact that an object can be found in nature. For example, a polypeptide or polynucleotide sequence that is present in an organism (including viruses) that can be isolated from a source in nature and which has not been intentionally modified by man in the laboratory is naturally-occurring.

"Amplification" is a special case of nucleic acid replication involving template specificity. It is to be contrasted with nonspecific template replication (i.e., replication that is template-dependent but not dependent on a specific template). Template specificity is here distinguished from fidelity of replication (i.e., synthesis of the proper polynucleotide sequence) and nucleotide (ribo- or deoxyribo) specificity. Template specificity is frequently described in terms of "target" specificity. Target sequences are "targets" in the sense that they are

sought to be sorted out from other nucleic acid. Amplification techniques have been designed primarily for this sorting out.

Template specificity is achieved in most amplification techniques by the choice of enzyme. Amplification enzymes are enzymes that, under conditions they are used, will process only specific sequences of nucleic acid in a heterogeneous mixture of nucleic acid. For example, in the case of Q beta replicase, MDV-1 RNA is the specific template for the replicase (D. L. Kacian et al., Proc. Natl. Acad. Sci. USA 69:3038 (1972)). Other nucleic acids will not be replicated by this amplification enzyme. Similarly, in the case of T7 RNA polymerase, this amplification enzyme has a stringent specificity for its own promoters (Chamberlin et al., Nature 228:227 (1970)). In the case of T4 DNA ligase, the enzyme will not ligate the two oligonucleotides or polynucleotides, where there is a mismatch between the oligonucleotide or polynucleotide substrate and the template at the ligation junction (D. Y. Wu and R. B. Wallace, Genomics 4:560 (1989)). Finally, Taq and Pfu polymerases, by virtue of their ability to function at high temperature, are found to display high specificity for the sequences bounded and thus defined by the primers; the high temperature results in thermodynamic conditions that favor primer hybridization with the target sequences and not hybridization with non-target sequences (H. A. Erlich (ed.), PCR Technology, Stockton Press (1989)).

As used herein, the term "amplifiable nucleic acid" is used in reference to nucleic acids that may be amplified by any amplification method. It is contemplated that "amplifiable nucleic acid" will usually comprise "sample template."

As used herein, the term "sample template" refers to nucleic acid originating from a sample that is analyzed for the presence of "target" (defined below). In contrast, "background template" is used in reference to nucleic acid other than sample template that may or may not be present in a sample. Background template is most often inadvertent. It may be the result of carryover, or it may be due to the presence of nucleic acid contaminants sought to be purified away from the sample. For example, nucleic acids from organisms other than those to be detected may be present as background in a test sample.

As used herein, the term "primer" refers to an oligonucleotide, whether occurring naturally as in a purified restriction digest or produced synthetically, which is capable of acting as a point of initiation of synthesis when placed under conditions in which synthesis of a primer extension product which is complementary to a nucleic acid strand is induced, (i.e., in the presence of nucleotides and an inducing agent such as DNA polymerase and at a suitable temperature and pH). The primer is preferably single stranded for maximum efficiency in amplification, but may alternatively be double stranded. If double stranded, the primer is first treated to separate its strands before being used to prepare extension products. Preferably, the primer is an oligodeoxyribonucleotide. The primer must be sufficiently long to prime the synthesis of extension products in the presence of the inducing agent. The exact lengths of the primers will depend on many factors, including temperature, source of primer and the use of the method.

As used herein, the term "probe" refers to an oligonucleotide (i. e., a sequence of nucleotides), whether occurring naturally as in a purified restriction digest or produced synthetically, recombinantly or by PCR amplification, that is capable of hybridizing to another oligonucleotide of interest. A probe may be single-stranded or double-stranded. Probes are useful in the detection, identification and isolation of particular gene sequences. It is contemplated that any probe used in the present invention may be labeled with any "reporter molecule," so that is detectable in any detection system, including, but not limited to enzyme (e.g., ELISA, as well as enzyme-based histochemical assays), fluorescent, radioactive, and

luminescent systems. It is not intended that the present invention be limited to any particular detection system or label.

As used herein, the term "target," refers to a nucleic acid sequence or structure to be detected or characterized. Thus, the "target" is sought to be sorted out from other nucleic acid sequences. A "segment" is defined as a region of nucleic acid within the target sequence.

As used herein, the term "polymerase chain reaction" ("PCR") refers to the method described by Kleppe, et al., J. Molecular Biology, 56, 1971, pp. 341-361, and in U.S. Pat. Nos. 4,683,195, 4,683,202, and 4,965,188, hereby incorporated by reference, that describe a method for increasing the concentration of a segment of a target sequence in a mixture of genomic DNA without cloning or purification. This process for amplifying the target sequence consists of introducing a large excess of two oligonucleotide primers to the DNA mixture containing the desired target sequence, followed by a precise sequence of thermal cycling in the presence of a DNA polymerase. The two primers are complementary to their respective strands of the double stranded target sequence. To effect amplification, the mixture is denatured and the primers then annealed to their complementary sequences within the target molecule. Following annealing, the primers are extended with a polymerase so as to form a new pair of complementary strands. The steps of denaturation, primer annealing, and polymerase extension can be repeated many times (i.e., denaturation, annealing and extension constitute one "cycle"; there can be numerous "cycles") to obtain a high concentration of an amplified segment of the desired target sequence. The length of the amplified segment of the desired target sequence is determined by the relative positions of the primers with respect to each other, and therefore, this length is a controllable parameter. By virtue of the repeating aspect of the process, the method is referred to as the "polymerase chain reaction" (hereinafter "PCR"). Because the desired amplified segments of the target sequence become the predominant sequences (in terms of concentration) in the mixture, they are said to be "PCR amplified."

With PCR, it is possible to amplify a single copy of a specific target sequence in genomic DNA to a level detectable by several different methodologies (e.g., hybridization with a labeled probe; incorporation of biotinylated primers followed by avidinenzyme conjugate detection ; incorporation of 32P-labeled deoxynucleotide triphosphates, such as dCTP or dATP, into the amplified segment). In addition to genomic DNA, any oligonucleotide or polynucleotide sequence can be amplified with the appropriate set of primer molecules. In particular, the amplified segments created by the PCR process itself are, themselves, efficient templates for subsequent PCR amplifications.

As used herein, the terms "PCR product," "PCR fragment," and "amplification product" refer to the resultant mixture of compounds after two or more cycles of the PCR steps of denaturation, annealing and extension are complete. These terms encompass the case where there has been amplification of one or more segments of one or more target sequences.

As used herein, the term "amplification reagents" refers to those reagents (deoxyribonucleotide triphosphates, buffer, etc.) , needed for amplification except for primers, nucleic acid template, and the amplification enzyme. Typically, amplification reagents along with other reaction components are placed and contained in a reaction vessel (test tube, microwell, etc.).

As used herein, the terms "restriction endonucleases" and "restriction enzymes" refer to bacterial enzymes, each of which cut double-stranded DNA at or near a specific nucleotide sequence.

As used herein, the term "antisense" is used in reference to RNA sequences that are complementary to a specific RNA sequence (e. g., MRNA). Antisense RNA may be produced by any method, including synthesis by

splicing the gene(s) of interest in a reverse orientation to a viral promoter that permits the synthesis of a coding strand. Once introduced into an embryo, this transcribed strand combines with natural mRNA produced by the embryo to form duplexes. These duplexes then block either the further transcription of the mRNA or its translation. In this manner, mutant phenotypes may be generated. The term "antisense strand" is used in reference to a nucleic acid strand that is complementary to the "sense" strand. The designation (-) (i.e., "negative") is sometimes used in reference to the antisense strand, with the designation (+) sometimes used in reference to the sense (i.e., "positive") strand.

The term "isolated" when used in relation to a nucleic acid, as in "an isolated oligonucleotide" or "isolated polynucleotide" refers to a nucleic acid sequence that is identified and separated from at least one contaminant nucleic acid with which it is ordinarily associated in its natural source. Isolated nucleic acid is present in a form or setting that is different from that in which it is found in nature. In contrast, nonisolated nucleic acids are nucleic acids such as DNA and RNA found in the state they exist in nature. For example, a given DNA sequence (e.g., a gene) is found on the host cell chromosome in proximity to neighboring genes; RNA sequences, such as a specific mRNA sequence encoding a specific protein, are found in the cell as a mixture with numerous other mRNAs that encode a multitude of proteins. However, isolated nucleic acid encoding LPH3 includes, by way of example, such nucleic acid in cells ordinarily expressing LPH3 (e.g. trabecular meshwork cells) where the nucleic acid is in a chromosomal location different from that of natural cells, or is otherwise flanked by a different nucleic acid sequence than that found in nature. The isolated nucleic acid, oligonucleotide, or polynucleotide may be present in single-stranded or doublestranded form. When an isolated nucleic acid, oligonucleotide or polynucleotide is to be utilized to express a protein, the oligonucleotide or polynucleotide will contain at a minimum the sense or coding strand (i. e., the oligonucleotide or polynucleotide may single-stranded), but may contain both the sense and anti-sense strands (i.e., the oligonucleotide or polynucleotide may be double-stranded).

As used herein the term "portion" when in reference to a nucleotide sequence (as in "a portion of a given nucleotide sequence") refers to fragments of that sequence. The fragments may range in size from four nucleotides to the entire nucleotide sequence minus one nucleotide (10 nucleotides, 20, 30, 40, 50, 100, 200, etc.).

As used herein the term "coding region" when used in reference to structural gene refers to the nucleotide sequences that encode the amino acids found in the nascent polypeptide as a result of translation of a MRNA molecule. The coding region is bounded, in eukaryotes, on the 5' side by the nucleotide triplet "ATG" that encodes the initiator methionine and on the 3' side by one of the three triplets, which specify stop codons (i.e., TAA, TAG, TGA).

As used herein, the term "purified" or "to purify" refers to the removal of contaminants from a sample. For example, LPH3 antibodies are purified by removal of contaminating nonimmunoglobulin proteins; they are also purified by the removal of immunoglobulin that does not bind LPH3. The removal of nonimmunoglobulin proteins and/or the removal of immunoglobulins that do not bind LPH3 results in an increase in the percent of LPH3-reactive immunoglobulins in the sample. In another example, recombinant LPH3 polypeptides are expressed in bacterial host cells and the polypeptides are purified by the removal of host cell proteins; the percent of recombinant LPH3 polypeptides is thereby increased in the sample.

The term "recombinant DNA molecule" as used herein refers to a DNA molecule that is comprised of segments of DNA joined together by means of molecular biological techniques.

The term "recombinant protein" or "recombinant polypeptide" as used herein

refers to a protein molecule that is expressed from a recombinant DNA molecule.

The term "native protein" as used herein to indicate that a protein does not contain amino acid residues encoded by vector sequences; that is the native protein contains only those amino acids found in the protein as it occurs in nature. A native protein may be produced by recombinant means or may be isolated from a naturally occurring source.

The term "Southern blot," refers to the analysis of DNA on agarose or acrylamide gels to fractionate the DNA according to size followed by transfer of the DNA from the gel to a solid support, such as nitrocellulose or a nylon membrane. The immobilized DNA is then probed with a labeled probe to detect DNA species complementary to the probe used. The DNA may be cleaved with restriction enzymes prior to electrophoresis. Following electrophoresis, the DNA may be partially depurinated and denatured prior to or during transfer to the solid support. Southern blots are a standard tool of molecular biologists (J. Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, NY, pp 9.31-9.58 (1989)).

The term "Northern blot," as used herein refers to the analysis of RNA by electrophoresis of RNA on agarose gels to fractionate the RNA according to size followed by transfer of the RNA from the gel to a solid support, such as nitrocellulose or a nylon membrane. The immobilized RNA is then probed with a labeled probe to detect RNA species complementary to the probe used. Northern blots are a standard tool of molecular biologists (J. Sambrook, et al, supra, pp 7.39-7.52 (1989)).

The term "Western blot" refers to the analysis of protein(s) (or polypeptides) immobilized onto a support such as nitrocellulose or a membrane. The proteins are run on acrylamide gels to separate the proteins, followed by transfer of the protein from the gel to a solid support, such as nitrocellulose or a nylon membrane. The immobilized proteins are then exposed to antibodies with reactivity against an antigen of interest. The binding of the antibodies may be detected by various methods, including the use of radiolabelled antibodies.

The term "antigenic determinant" as used herein refers to that portion of an antigen that makes contact with a particular antibody (i.e., an epitope). When a protein or fragment of a protein is used to immunize a host animal, numerous regions of the protein may induce the production of antibodies that bind specifically to a given region or three-dimensional structure on the protein; these regions or structures are referred to as antigenic determinants. An antigenic determinant may compete with the intact antigen (i.e., the "immunogen" used to elicit the immune response) for binding to an antibody.

The term "transgene" as used herein refers to a foreign, heterologous, or autologous gene that is placed into an organism by introducing the gene into newly fertilized eggs or early embryos. The term "foreign gene" refers to any nucleic acid (e.g., gene sequence) that is introduced into the genome of an animal by experimental manipulations and may include gene sequences found in that animal so long as the introduced gene does not reside in the same location as does the naturallyoccurring gene. The term "autologous gene" is intended to encompass variants (e.g., polymorphisms or mutants) of the naturally occurring gene. The term transgene thus encompasses the replacement of the naturally occurring gene with a variant form of the gene.

As used herein, the term "vector" is used in reference to nucleic acid molecules that transfer DNA segment(s) from one cell to another. The term "vehicle" is sometimes used interchangeably with "vector."

The term "expression vector" as used herein refers to a recombinant DNA molecule containing a desired coding sequence and appropriate nucleic acid sequences necessary for the expression of the operably linked coding sequence in a particular host organism. Nucleic acid sequences necessary for expression in prokaryotes usually include a promoter, an operator

(optional), and a ribosome binding site, often along with other sequences. Eukaryotic cells are known to utilize promoters, enhancers, and termination and polyadenylation signals.

As used herein, the term "host cell" refers to any eukaryotic or prokaryotic cell (e.g., bacterial cells such as E. coli, yeast cells, mammalian cells, avian cells, amphibian cells, plant cells, fish cells, and insect cells), whether located in vitro or in vivo. For example, host cells may be located in a transgenic animal.

The terms "overexpression" and "overexpressing" and grammatical equivalents, are used in reference to levels of mRNA to indicate a level of expression approximately 3-fold higher than that typically observed in a given tissue in a control or nontransgenic animal. Levels of mRNA are measured using any of a number of techniques known to those skilled in the art including, but not limited to Northern blot analysis (See, Example 10, for a protocol for performing Northern blot analysis). Appropriate controls are included on the Northern blot to control for differences in the amount of RNA loaded from each tissue analyzed (e.g., the amount of 28S rRNA, an abundant RNA transcript present at essentially the same amount in all tissues, present in each sample can be used as a means of normalizing or standardizing the RAD50 mRNA-specific signal observed on Northern blots). The amount of MRNA present in the band corresponding in size to the correctly spliced LPH (e.g. human LPH3) transgene RNA is quantified; other minor species of RNA which hybridize to the transgene probe are not considered in the quantification of the expression of the transgenic mRNA.

The term "transfection" as used herein refers to the introduction of foreign DNA into eukaryotic cells. Transfection may be accomplished by a variety of means known to the art including calcium phosphate-DNA co-precipitation, DEAE-dextranmediated transfection, polybrene-mediated transfection, electroporation, microinjection, liposome fusion, lipofection, protoplast fusion, retroviral infection, and biolistics.

The term "stable transfection" or "stably transfected" refers to the introduction and integration of foreign DNA into the genome of the transfected cell. The term "stable transfectant" refers to a cell that has stably integrated foreign DNA into the genomic DNA.

The term "transient transfection" or "transiently transfected" refers to the introduction of foreign DNA into a cell where the foreign DNA fails to integrate into the genome of the transfected cell. The foreign DNA persists in the nucleus of the transfected cell for several days. During this time the foreign DNA is subject to the regulatory controls that govern the expression of endogenous genes in the chromosomes. The term "transient transfectant" refers to cells that have taken up foreign DNA but have failed to integrate this DNA.

The term "calcium phosphate co-precipitation" refers to a technique for the introduction of nucleic acids into a cell. The uptake of nucleic acids by cells is enhanced when the nucleic acid is presented as a calcium phosphate-nucleic acid co-precipitate. The original technique of Graham and van der Eb (Graham and van der Eb, Virol., 52:456 (1973)), has been modified by several groups to optimize conditions for particular types of cells. The art is well aware of these numerous modifications.

A "composition comprising a given polynucleotide sequence" as used herein refers broadly to any composition containing the given polynucleotide sequence. The composition may comprise an aqueous solution. Compositions comprising polynucleotide sequences encoding LPH3 (e.g., SEQ ID NO:1) or fragments thereof may be employed as hybridization probes. In this case, the LPH3 encoding polynucleotide sequences are typically employed in an aqueous solution containing salts (e.g., NaCl), detergents (e.g., SDS), and other components (e.g., Denhardt's solution, dry milk, salmon sperm DNA, etc.).

The term "test compound" or "candidate compound" refer to any chemical entity, pharmaceutical, drug, and the like that can be used to treat or

prevent a disease, illness, sickness, or disorder of bodily function, or otherwise alter the physiological or cellular status of a sample. Test compounds comprise both known and potential therapeutic compounds. A test compound can be determined to be therapeutic by screening using the screening methods of the present invention. A "known therapeutic compound" refers to a therapeutic compound that has been shown (e.g., through animal trials or prior experience with administration to humans) to be effective in such treatment or prevention.

As used herein, the term "response," when used in reference to an assay, refers to the generation of a detectable signal (e.g., accumulation of reporter protein, increase in ion concentration, accumulation of a detectable chemical product).

As used herein, the term "reporter gene" refers to a gene encoding a protein that may be assayed. Examples of reporter genes include, but are not limited to, luciferase (See, e.g., deWet et al., Mol. Cell. Biol. 7:725 (1987) and U.S. Pat Nos., 6,074,859, incorporated herein by reference), green fluorescent protein (e.g., GenBank Accession Number U43284; a number of GFP variants are commercially available from CLONTECH Laboratories, Palo Alto, Calif.), chloramphenicol acetyltransferase, betagalactosidase, alkaline phosphatase, and horse radish peroxidase.

As used herein, the terms "computer memory" and "computer memory device" refer to any storage media readable by a computer processor. Examples of computer memory include, but are not limited to, RAM, ROM, computer chips, digital video disc (DVDs), compact discs (CDs), hard disk drives (HDD), and magnetic tape.

As used herein, the term "computer readable medium" refers to any device or system for storing and providing information (e.g. , data and instructions) to a computer processor. Examples of computer readable media include, but are not limited to, DVDs, CDs, hard disk drives, magnetic tape and servers for streaming media over networks.

As used herein, the phrase "computer readable medium encodes a representation" of a nucleic acid or amino acid sequence, refers to computer readable medium that has stored thereon information, that when delivered to a processor, allows the sequence of the nucleic or amino acid sequence to be displayed to a user (e.g. printed out or presented on a display screen).

As used herein, the terms "processor" and "central processing unit" or "CPU" are used interchangeably and refer to a device that is able to read a program from a computer memory (e.g., ROM or other computer memory) and perform a set of steps according to the program. !

L8 ANSWER 40 OF 71 USPATFULL on STN DUPLICATE 2

ACCESSION NUMBER: 2002:337319 USPATFULL <<LOGINID::20080318>>

TITLE: Nucleic acid amplification with DNA-dependent RNA polymerase activity of RNA replicases

INVENTOR(S): Dimond, Randall L., Madison, WI, UNITED STATES
Ekenberg, Steven J., Mt. Horeb, WI, UNITED STATES
Hartnett, James R., Madison, WI, UNITED STATES
Hudson, Geoffrey R., Madison, WI, UNITED STATES
Mendoza, Leopoldo G., Madison, WI, UNITED STATES
Miller, Katharine M., Verona, WI, UNITED STATES
Monahan, John E., Walpole, MA, UNITED STATES
Jones, Christopher L., Madison, WI, UNITED STATES
Maffitt, Mark A., Madison, WI, UNITED STATES
Martinelli, Richard A., Brighton, MA, UNITED STATES
Pahuski, Edward E., Marshall, WI, UNITED STATES
Schumm, James W., Madison, WI, UNITED STATES

PATENT ASSIGNEE(S): Promega Corporation (U.S. corporation)

	NUMBER	KIND	DATE

PATENT INFORMATION: US 2002192677 A1 20021219
US 6677140 B2 20040113
APPLICATION INFO.: US 2002-71057 A1 20020207 (10)
RELATED APPLN. INFO.: Division of Ser. No. US 1999-396001, filed on 14 Sep 1999, GRANTED, Pat. No. US 6369207 Continuation of Ser. No. US 1995-480041, filed on 6 Jun 1995, GRANTED, Pat. No. US 6090589 Continuation-in-part of Ser. No. US 1990-638508, filed on 31 Dec 1990, ABANDONED
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: FOLEY & LARDNER, 150 EAST GILMAN STREET, P.O. BOX 1497, MADISON, WI, 53701-1497
NUMBER OF CLAIMS: 78
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 10 Drawing Page(s)
LINE COUNT: 3689
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention entails methods, and kits for carrying them out, based on the discovery that an RNA replicase, such as Qβ replicase, has DNA-dependent RNA polymerase ("DDRP") activity with nucleic acid segments, including DNA segments and DNA:RNA chimeric segments, which comprise a 2'-deoxyribonucleotide or an analog thereof and which have sequences of RNAs that are autocatalytically replicatable by the replicase. The discovery of this DDRP activity provides methods of the invention for nucleic acid amplification wherein a nucleic acid, with a DNA segment with the sequence of an RNA that is autocatalytically replicatable by an RNA replicase, is provided as a substrate for the replicase. The replicase catalyzes synthesis, from the DNA segment, of the RNA, which the replicase then autocatalytically replicates. The invention entails use of the amplification methods in detecting nucleic acid analytes, as in nucleic acid probe hybridization assays. Such assays of the invention include those wherein a nucleic acid analyte is hybridized with one or more nucleic acid probes, which include or are processed to generate a DNA segment which is amplifiable through production from the segment, catalyzed by the DDRP activity of an RNA replicase, of an autocatalytically replicatable RNA, which is autocatalytically replicated to provide an abundance of readily detectable reporter molecules. The invention permits replacement of an RNA, that is autocatalytically replicatable with an RNA replicase and employed as a reporter or label in prior art assays, such as nucleic acid probe hybridization assays or immunoassays, with a nucleic acid comprising a DNA segment with the same base sequence as the RNA. The invention also includes the methods of the invention with Mn.sup.+2, Co.sup.+2, or Zn.sup.+2 in the solutions in which the DDRP activity occurs.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 41 OF 71 USPATFULL on STN DUPLICATE 3
ACCESSION NUMBER: 2002:32165 USPATFULL <<LOGINID::20080318>>
TITLE: Method for the detection of the presence of chemical species known to inhibit a chemiluminescent reaction
INVENTOR(S): DiCesare, Joseph L., Redding, CT, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002018986	A1	20020214
	US 6541194	B2	20030401
APPLICATION INFO.:	US 2001-821806	A1	20010329 (9)

	NUMBER	DATE

PRIORITY INFORMATION:	US 2000-193519P	20000331 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	ST. ONGE STEWARD JOHNSTON & REENS, LLC, 986 BEDFORD STREET, STAMFORD, CT, 06905-5619	
NUMBER OF CLAIMS:	7	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	6 Drawing Page(s)	
LINE COUNT:	1508	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed herein is a method to detect the presence of potentially inhibitory species that could interfere with a chemiluminescent assay procedure for determination of an analyte of interest. According to the disclosed method, a surface to be analyzed for the presence of an analyte of interest is first sampled by wiping the surface with a polymeric sampling swab. The sample thus obtain is mixed with a known amount of the analyte of interest and the chemiluminescence generated by a reaction with a suitable reactant system is measured. The resultant emission level is then compared with the expected level of emission based on the known amount of the analyte of interest mixed with the sample. If the emission level is below that expected based on the known amount of analyte, then the sampled surface is contaminated with inhibitory species.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 42 OF 71 USPATFULL on STN DUPLICATE 4

ACCESSION NUMBER:	2002:3847 USPATFULL <<LOGINID::20080318>>			
TITLE:	Apparatus and methods for chemiluminescent assays			
INVENTOR(S):	DiCesare, Joseph L., Redding, CT, UNITED STATES			

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002001822	A1	20020103	
	US 6653147	B2	20031125	
APPLICATION INFO.:	US 2001-821149	A1	20010329	(9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-193519P	20000331 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	ST. ONGE STEWARD JOHNSTON & REENS, LLC, 986 BEDFORD STREET, STAMFORD, CT, 06905-5619
NUMBER OF CLAIMS:	28
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	6 Drawing Page(s)
LINE COUNT:	1557

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed herein are methods for the chemiluminescent assay of a variety of analytes of interest. The methods are adaptable to the determination of microbial species in both liquid samples and on solid surfaces. The disclosed methods can be used with rapid, self-contained chemiluminescence assay devices, or can be used with novel sampling devices and conventional microbial analysis techniques involving growth of microbial samples on appropriate culturing media. The specificity of the methods can be enhanced with the use of immunospecific reagents. The sensitivity of the technique can be increased by 3 to 6 orders of magnitude by first converting all DNA in the sample to inorganic phosphates before generating the emission signal. The breadth of

applicability of the disclosed methods can be enhanced through the selection of appropriate enzyme-catalyzed reactions where one of the products of enzymatic oxidation is hydrogen peroxide.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 43 OF 71 USPATFULL on STN DUPLICATE 5
ACCESSION NUMBER: 2002:3566 USPATFULL <<LOGINID::20080318>>
TITLE: Apparatus and methods for chemiluminescent assays
INVENTOR(S): DiCesare, Joseph L., Redding, CT, UNITED STATES
McCaffrey, John T., Cheshire, CT, UNITED STATES
Clark, David, Sandy Hook, CT, UNITED STATES
Crockett, Michael I., Newtown, CT, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002001539	A1	20020103
	US 6548018	B2	20030415
APPLICATION INFO.:	US 2001-821148	A1	20010329 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-193519P	20000331 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: ST. ONGE STEWARD JOHNSTON & REENS, LLC, 986 BEDFORD STREET, STAMFORD, CT, 06905-5619
NUMBER OF CLAIMS: 40
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 6 Drawing Page(s)
LINE COUNT: 1631
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Disclosed herein is a device and methods for the rapid chemiluminescence assay of surfaces to detect the presence of microbial contamination. The device and methods are suitable for use by untrained personnel under the relatively harsh and variable conditions found in the field, for example in fast food restaurants and other food preparation areas. The chemiluminescence reaction that is the source of the analytical signal in the disclosed assay device and method is preferably based on a luciferase/luciferin system. The method for sampling disclosed herein comprises the steps of pre-wetting the sampling swab to a level below that of absorptive saturation; wiping a surface to be sampled with the swab with sufficient pressure to expel the wetting solution onto the surface; and, after reducing the pressure exerted on the sampling swab, further wiping the surface to re-absorb the moisture from the surface.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 44 OF 71 USPATFULL on STN
ACCESSION NUMBER: 2002:315083 USPATFULL <<LOGINID::20080318>>
TITLE: Nucleic acid sequences associated with baldness
INVENTOR(S): Pritchard, David, Seattle, WA, UNITED STATES
Burmer, Glenna, Seattle, WA, UNITED STATES
Brown, Joseph, Seattle, WA, UNITED STATES
Demas, Vasiliki, Seattle, WA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002177566	A1	20021128
APPLICATION INFO.:	US 2001-825096	A1	20010402 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-199745P	20000425 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: TOWNSEND AND TOWNSEND AND CREW, LLP, TWO EMBARCADERO CENTER, EIGHTH FLOOR, SAN FRANCISCO, CA, 94111-3834
NUMBER OF CLAIMS: 25
EXEMPLARY CLAIM: 1
LINE COUNT: 3768
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention relates to the discovery of nucleic acids and proteins associated with baldness and/or hair loss. The identification of these baldness-associated nucleic acids and proteins have uses in predicting the propensity for baldness of an individual and/or in determining the likelihood of baldness in an individual experiencing hair loss. In addition, the nucleic acids of the invention can be used can be used for gene therapy for delaying or stopping the progression of baldness, and/or for reversing baldness.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 45 OF 71 USPATFULL on STN
ACCESSION NUMBER: 2002:301080 USPATFULL <<LOGINID::20080318>>
TITLE: Compositions and methods for induction of proteins involved in xenobiotic metabolism
INVENTOR(S): Raucy, Judy, San Diego, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002168623	A1	20021114
APPLICATION INFO.:	US 2001-832621	A1	20010411 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-196681P	20000412 (60)
	US 2000-241391P	20001017 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: DAVID R PRESTON & ASSOCIATES, 12625 HIGH BLUFF DRIVE, SUITE 205, SAN DIEGO, CA, 92130
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 24 Drawing Page(s)
LINE COUNT: 2077
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides improved cells and methods for identifying compounds that alter protein expression, such as xenobiotics, endobiotics, chemicals or drugs. The invention provides other benefits as well. One aspect of the present invention is a cell that includes a first nucleic acid molecule that includes: a promoter or enhancer operable for a nucleic acid molecule encoding a protein involved in drug metabolism (such as an enzyme or transporter) and a reporter gene; and a second nucleic acid encoding an intracellular receptor or transcription factor; so that when the intracellular receptor or transcription factor is bound with a compound, the intracellular receptor, transporter or transcription factor can operably bind with the promoter or enhancer resulting in the expression of said reporter gene. Another aspect of the present invention is a method for evaluating compounds for the property of inducing the expression of a

gene encoding a protein involved in drug metabolism, including; providing a test compound; contacting the test compound with a cell of the present invention; and detecting the expression of said reporter gene. This method can be a high throughput method.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 46 OF 71 USPATFULL on STN

ACCESSION NUMBER:	2002:294666 USPATFULL <<LOGINID::20080318>>
TITLE:	Nucleic acid endocing growth factor protein
INVENTOR(S):	Shigeta, Ron T., JR., Berkeley, CA, UNITED STATES Siani-Rose, Michael A., San Francisco, CA, UNITED STATES
PATENT ASSIGNEE(S):	Affymetrix, INC. A corporation organized under the laws of Delaware (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002164709	A1	20021107
APPLICATION INFO.:	US 2002-83853	A1	20020226 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-272663P	20010301 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	AFFYMETRIX, INC, ATTN: CHIEF IP COUNSEL, LEGAL DEPT., 3380 CENTRAL EXPRESSWAY, SANTA CLARA, CA, 95051
NUMBER OF CLAIMS:	48
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	10 Drawing Page(s)
LINE COUNT:	2816

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides a novel growth factor polynucleotide, growth factor polypeptide, gene delivery vehicles comprising and/or expressing the growth factor polynucleotide, antibodies and fragments capable of specifically binding to the growth factor polypeptide, receptors of the growth factor polypeptide, modulators of the growth factor activity, and modulators of growth factor expression. Also provided by the invention are host cells and transgenic organisms comprising the gene delivery vehicle of the present invention. Also provided by the invention are computer readable media containing the polynucleotide or polypeptide sequences of the present invention. Further provided are methods of using these compositions for diagnosis and treatment of growth factor associated diseases.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 47 OF 71 USPATFULL on STN

ACCESSION NUMBER:	2002:272801 USPATFULL <<LOGINID::20080318>>
TITLE:	Compositions and methods for the therapy and diagnosis of colon cancer
INVENTOR(S):	Stolk, John A., Bothell, WA, UNITED STATES Xu, Jiangchun, Bellevue, WA, UNITED STATES Chenault, Ruth A., Seattle, WA, UNITED STATES Meagher, Madeleine Joy, Seattle, WA, UNITED STATES
PATENT ASSIGNEE(S):	Corixa Corporation, Seattle, WA, UNITED STATES, 98104 (U.S. corporation)

	NUMBER	KIND	DATE

PATENT INFORMATION: US 2002150922 A1 20021017
APPLICATION INFO.: US 2001-998598 A1 20011116 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-304037P	20010710 (60)
	US 2001-279670P	20010328 (60)
	US 2001-267011P	20010206 (60)
	US 2000-252222P	20001120 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: SEED INTELLECTUAL PROPERTY LAW GROUP PLLC, 701 FIFTH AVE, SUITE 6300, SEATTLE, WA, 98104-7092
NUMBER OF CLAIMS: 17
EXEMPLARY CLAIM: 1
LINE COUNT: 9233
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Compositions and methods for the therapy and diagnosis of cancer, particularly colon cancer, are disclosed. Illustrative compositions comprise one or more colon tumor polypeptides, immunogenic portions thereof, polynucleotides that encode such polypeptides, antigen presenting cell that expresses such polypeptides, and T cells that are specific for cells expressing such polypeptides. The disclosed compositions are useful, for example, in the diagnosis, prevention and/or treatment of diseases, particularly colon cancer.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 48 OF 71 USPATFULL on STN
ACCESSION NUMBER: 2002:243051 USPATFULL <<LOGINID::20080318>>
TITLE: Compositions and methods for the therapy and diagnosis of ovarian cancer
INVENTOR(S): Algate, Paul A., Issaquah, WA, UNITED STATES
Jones, Robert, Seattle, WA, UNITED STATES
Harlocker, Susan L., Seattle, WA, UNITED STATES
PATENT ASSIGNEE(S): Corixa Corporation, Seattle, WA, UNITED STATES, 98104 (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002132237	A1	20020919
APPLICATION INFO.:	US 2001-867701	A1	20010529 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-207484P	20000526 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: SEED INTELLECTUAL PROPERTY LAW GROUP PLLC, 701 FIFTH AVE, SUITE 6300, SEATTLE, WA, 98104-7092
NUMBER OF CLAIMS: 11
EXEMPLARY CLAIM: 1
LINE COUNT: 25718
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Compositions and methods for the therapy and diagnosis of cancer, particularly ovarian cancer, are disclosed. Illustrative compositions comprise one or more ovarian tumor polypeptides, immunogenic portions thereof, polynucleotides that encode such polypeptides, antigen presenting cell that expresses such polypeptides, and T cells that are specific for cells expressing such polypeptides. The disclosed compositions are useful, for example, in the diagnosis, prevention

and/or treatment of diseases, particularly ovarian cancer.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 49 OF 71 USPATFULL on STN

ACCESSION NUMBER:	2002:242791 USPATFULL <<LOGINID::20080318>>
TITLE:	Compositions and methods for the therapy and diagnosis of colon cancer
INVENTOR(S):	King, Gordon E., Shoreline, WA, UNITED STATES Meagher, Madeleine Joy, Seattle, WA, UNITED STATES Xu, Jiangchun, Bellevue, WA, UNITED STATES Secrist, Heather, Seattle, WA, UNITED STATES
PATENT ASSIGNEE(S):	Corixa Corporation, Seattle, WA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002131971	A1	20020919
APPLICATION INFO.:	US 2001-33528	A1	20011226 (10)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2001-920300, filed on 31 Jul 2001, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-302051P	20010629 (60)
	US 2001-279763P	20010328 (60)
	US 2000-223283P	20000803 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	SEED INTELLECTUAL PROPERTY LAW GROUP PLLC, 701 FIFTH AVE, SUITE 6300, SEATTLE, WA, 98104-7092
NUMBER OF CLAIMS:	17
EXEMPLARY CLAIM:	1
LINE COUNT:	8083

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compositions and methods for the therapy and diagnosis of cancer, particularly colon cancer, are disclosed. Illustrative compositions comprise one or more colon tumor polypeptides, immunogenic portions thereof, polynucleotides that encode such polypeptides, antigen presenting cell that expresses such polypeptides, and T cells that are specific for cells expressing such polypeptides. The disclosed compositions are useful, for example, in the diagnosis, prevention and/or treatment of diseases, particularly colon cancer.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 50 OF 71 USPATFULL on STN

ACCESSION NUMBER:	2002:235434 USPATFULL <<LOGINID::20080318>>
TITLE:	Biosensors, reagents and diagnostic applications of directed evolution
INVENTOR(S):	Minshull, Jeremy, Menlo Park, CA, UNITED STATES Davis, S. Christopher, San Francisco, CA, UNITED STATES Welch, Mark, Fremont, CA, UNITED STATES Raillard, Sun Ai, Mountain View, CA, UNITED STATES Vogel, Kurt, Palo Alto, CA, UNITED STATES Krebber, Claus, Mountain View, CA, UNITED STATES
PATENT ASSIGNEE(S):	Maxygen, Inc., Redwood City, CA (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002127623	A1	20020912

APPLICATION INFO.: US 2001-920607 A1 20010731 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-222056P	20000731 (60)
	US 2000-244764P	20001031 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: LAW OFFICES OF JONATHAN ALAN QUINE, P O BOX 458, ALAMEDA, CA, 94501
NUMBER OF CLAIMS: 130
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 7 Drawing Page(s)
LINE COUNT: 6877
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Methods for sensing test stimuli using arrays of biopolymers are provided. Libraries of biopolymers, such nucleic acid variants, and expression products encoded by nucleic acid variants are provided. Reusable library arrays, and methods for their use are provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 51 OF 71 USPATFULL on STN
ACCESSION NUMBER: 2002:227930 USPATFULL <<LOGINID::20080318>>
TITLE: Nucleic acid endocing growth factor protein
INVENTOR(S): Shigeta, Ron T., JR., Berkeley, CA, UNITED STATES
Siani-Rose, Michael A., San Francisco, CA, UNITED STATES
PATENT ASSIGNEE(S): Affymetrix, INC. (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002123083	A1	20020905
APPLICATION INFO.:	US 2002-84037	A1	20020226 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-272662P	20010301 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: AFFYMETRIX, INC, ATTN: CHIEF IP COUNSEL, LEGAL DEPT., 3380 CENTRAL EXPRESSWAY, SANTA CLARA, CA, 95051
NUMBER OF CLAIMS: 48
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 3 Drawing Page(s)
LINE COUNT: 2402
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides a novel growth factor polynucleotide, growth factor polypeptide, gene delivery vehicles comprising and/or expressing the growth factor polynucleotide, antibodies and fragments capable of specifically binding to the growth factor polypeptide, receptors of the growth factor polypeptide, modulators of the growth factor activity, and modulators of growth factor expression. Also provided by the invention are host cells and transgenic organisms comprising the gene delivery vehicle of the present invention. Also provided by the invention are computer readable media containing the polynucleotide or polypeptide sequences of the present invention. Further provided are methods of using these compositions for diagnosis and treatment of growth factor associated diseases.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 52 OF 71 USPATFULL on STN
ACCESSION NUMBER: 2002:185583 USPATFULL <<LOGINID::20080318>>
TITLE: Proteins associated with aging
INVENTOR(S): Burmer, Glenna, Seattle, WA, UNITED STATES
Pritchard, David, Seattle, WA, UNITED STATES
Brown, Joseph P., Seattle, WA, UNITED STATES
Demas, Vasiliki, Seattle, WA, UNITED STATES
PATENT ASSIGNEE(S): LifeSpan BioSciences, Inc., Seattle, WA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002098495	A1	20020725
APPLICATION INFO.:	US 2001-898730	A1	20010703 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-216470P	20000706 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: TOWNSEND AND TOWNSEND AND CREW, LLP, TWO EMBARCADERO CENTER, EIGHTH FLOOR, SAN FRANCISCO, CA, 94111-3834
NUMBER OF CLAIMS: 17
EXEMPLARY CLAIM: 1
LINE COUNT: 3023
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to the discovery of nucleic acids and proteins associated with the aging processes, such as cell proliferation and senescence. The identification of these aging-associated nucleic acids and proteins have diagnostic uses in detecting the aging status of a cell population as well as applications for gene therapy and the delaying of the aging process.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 53 OF 71 USPATFULL on STN
ACCESSION NUMBER: 2002:22092 USPATFULL <<LOGINID::20080318>>
TITLE: Nucleic acid sequences associated wih aging, particularly skin aging
INVENTOR(S): Burmer, Glenna C., Seattle, WA, UNITED STATES
Brown, Joseph P., Seattle, WA, UNITED STATES
Pritchard, David, Seattle, WA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002012927	A1	20020131
APPLICATION INFO.:	US 2001-802718	A1	20010308 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-188584P	20000310 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: TOWNSEND AND TOWNSEND AND CREW, TWO EMBARCADERO CENTER, EIGHTH FLOOR, SAN FRANCISCO, CA, 94111-3834
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
LINE COUNT: 2368
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to the discovery of nucleic acids and proteins

associated with the aging processes, such as cell proliferation and senescence, and in particular with skin aging. The identification of these aging-associated nucleic acids and proteins have diagnostic uses in detecting the aging status of a cell population as well as application for gene therapy and the delaying of the aging process.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 54 OF 71 USPATFULL on STN

ACCESSION NUMBER:	2002:304068 USPATFULL <<LOGINID::20080318>>
TITLE:	Nucleoside triphosphates and their incorporation into oligonucleotides
INVENTOR(S):	Beigelman, Leonid, Longmont, CO, United States Burgin, Alex, Chula Vista, CA, United States Beaudry, Amber, Broomfield, CO, United States Karpeisky, Alexander, Lafayette, CO, United States Matulic-Adamic, Jasenka, Boulder, CO, United States Sweedler, David, Louisville, CO, United States Zinnen, Shawn, Denver, CO, United States
PATENT ASSIGNEE(S):	Ribozyme Pharmaceuticals, Incorporated, Boulder, CO, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6482932	B1	20021119
APPLICATION INFO.:	US 1999-301511		19990428 (9)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1998-186675, filed on 4 Nov 1998, now patented, Pat. No. US 6127535		

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-83727P	19980429 (60)
	US 1997-64866P	19971105 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	GRANTED
PRIMARY EXAMINER:	Richter, Johann
ASSISTANT EXAMINER:	Crane, Lawrence E
LEGAL REPRESENTATIVE:	McDonnell Boehnen Hulbert & Berghoff
NUMBER OF CLAIMS:	20
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	8 Drawing Figure(s); 9 Drawing Page(s)
LINE COUNT:	2639

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Novel nucleotide triphosphates, methods of synthesis and process of incorporating these nucleotide triphosphates into oligonucleotides, and isolation of novel nucleic acid catalysts (e.g., ribozymes) are disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 55 OF 71 USPATFULL on STN

ACCESSION NUMBER:	2002:75566 USPATFULL <<LOGINID::20080318>>
TITLE:	Nucleic acid amplification with DNA-dependent RNA polymerase activity of RNA replicases
INVENTOR(S):	Dimond, Randall L., Madison, WI, United States Ekenberg, Steven J., Mt. Horeb, WI, United States Hartnett, James R., Madison, WI, United States Hudson, Geoffrey R., Madison, WI, United States Mendoza, Leopoldo G., Madison, WI, United States Miller, Katharine M., Verona, WI, United States Monahan, John E., Walpole, MA, United States

Jones, Christopher L., Madison, WI, United States
Maffitt, Mark A., Madison, WI, United States
Martinelli, Richard A., Brighton, MA, United States
Pahuski, Edward E., Marshall, WI, United States
Schumm, James W., Madison, WI, United States
PATENT ASSIGNEE(S): Promega Corporation, Madison, WI, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6369207	B1	20020409
APPLICATION INFO.:	US 1999-396001		19990914 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1995-480041, filed on 6 Jun 1995, now patented, Pat. No. US 6090589
Continuation-in-part of Ser. No. US 1990-638508, filed on 31 Dec 1990, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Riley, Jezia
LEGAL REPRESENTATIVE: Foley & Lardner
NUMBER OF CLAIMS: 11
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 10 Drawing Figure(s); 10 Drawing Page(s)
LINE COUNT: 3232
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention entails methods, and kits for carrying them out, based on the discovery that an RNA replicase, such as Qβ replicase, has DNA-dependent RNA polymerase ("DDRP") activity with nucleic acid segments, including DNA segments and DNA:RNA chimeric segments, which comprise a 2'-deoxyribonucleotide or an analog thereof and which have sequences of RNAs that are autocatalytically replicatable by the replicase. The discovery of this DDRP activity provides methods of the invention for nucleic acid amplification wherein a nucleic acid, with a DNA segment with the sequence of an RNA that is autocatalytically replicatable by an RNA replicase, is provided as a substrate for the replicase. The replicase catalyzes synthesis, from the DNA segment, of the RNA, which the replicase then autocatalytically replicates. The invention entails use of the amplification methods in detecting nucleic acid analytes, as in nucleic acid probe hybridization assays. Such assays of the invention include those wherein a nucleic acid analyte is hybridized with one or more nucleic acid probes, which include or are processed to generate a DNA segment which is amplifiable through production from the segment, catalyzed by the DDRP activity of an RNA replicase, of an autocatalytically replicatable RNA, which is autocatalytically replicated to provide an abundance of readily detectable reporter molecules. The invention permits replacement of an RNA, that is autocatalytically replicatable with an RNA replicase and employed as a reporter or label in prior art assays, such as nucleic acid probe hybridization assays or immunoassays, with a nucleic acid comprising a DNA segment with the same base sequence as the RNA. The invention also includes the methods of the invention with Mn.sup.+2, Co.sup.+2, or Zn.sup.+2 in the solutions in which the DDRP activity occurs.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 56 OF 71 BIOTECHDS COPYRIGHT 2008 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2003-05023 BIOTECHDS <<LOGINID::20080318>>
TITLE: New Major Histocompatibility Complex (MHC) molecule construct, useful for treating, preventing, stabilizing or alleviating a disease involving MHC recognizing cells e.g.,

cancer;
major histocompatibility complex molecule construct and antibody use in disease gene therapy

AUTHOR: WINTHER L; PETERSEN L O; BUUS S; SCHOELLER J; RUUB E; AAMELLEM O

PATENT ASSIGNEE: DAKOCYTOMATION DENMARK AS; DYNAL BIOTECH ASA

PATENT INFO: WO 2002072631 19 Sep 2002

APPLICATION INFO: WO 2002-DK169 13 Mar 2002

PRIORITY INFO: US 2001-275470 14 Mar 2001; DK 2001-435 14 Mar 2001

DOCUMENT TYPE: Patent

LANGUAGE: English

OTHER SOURCE: WPI: 2002-759837 [82]

AN 2003-05023 BIOTECHDS <<LOGINID::20080318>>

AB DERWENT ABSTRACT:

NOVELTY - A new Major Histocompatibility Complex (MHC) molecule construct comprising a carrier molecule to which one or more MHC molecules are attached either directly or via one or more entities, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) detecting the presence or MHC recognizing cells in a sample; (2) monitoring MHC recognizing cells; (3) establishing a prognosis of a disease involving MHC recognizing cells; (4) determining the status of, or the effectiveness of a medicament against, a disease involving MHC recognizing cells; (5) diagnosing a disease involving MHC recognizing cells; (6) a therapeutic composition comprising as active ingredient a MHC molecule construct; (7) up-regulating, down-regulating or modulating an immune response in an animal, including a human being; (8) treating an animal, including a human being; (9) inducing energy of a cell in animal, including a human being; (10) an adoptive cellular immunotherapeutic method; (11) obtaining MHC recognizing cells; or (12) producing a therapeutic composition.

BIOTECHNOLOGY - Preferred Construct: The MHC molecule construct is in soluble form in a solubilizing medium. It is immobilized directly onto a biodegradable solid or semi-solid support via a linker, a spacer, or antibody or antibody derivative or its fragment, prior to expansion. The expansion is carried out in the presence of one or more MHC molecule constructs, optionally one or more biologically active molecules and optionally feeder cells such as dendritic cells or feeder cells. The support is selected from glass or chamber slides, dishes or petridishes microtiter plates having one or more wells, particles, beads, biodegradable particles, sheets, gels, filters, membranes (e. g. nylon or polymer membranes), fibers, capillaries, needles, microtiter strips, tubes, plates or wells, combs, pipette tips, micro arrays or chips. Preferably, the support is selected from beads and particles, which are polymeric beads, polymeric particles, magnetic beads, magnetic particles, supermagnetic beads or particles. The MHC molecule construct comprises peptide free or filled MHC molecules. The total number of MHC molecules of the construct is from 1 - 25, 1 - 50 or 1 - 100. The peptides to fill the peptide free MHC molecules, and the MHC molecule construct comprising peptide free molecules are provided separately. The MHC molecule construct further comprises one or more biologically active molecules selected from proteins, co-stimulatory molecules, cell modulating molecules, receptors, accessory molecules, adhesion molecules, natural ligands, toxic molecules, antibodies, recombinant binding molecules or their combinations. The biologically active molecules also comprises: (1) proteins such as MHC Class I-like proteins like MIC A, MIC B, CDld, human leukocyte antigen (HLA) E, HLA F, HLA G, HLA H, ULBP-1, ULBP-2, and ULBP-3; (2) co-stimulatory molecules such as CD2, CD3, CD4, CD5, CD8, CD9, CD27, CD28, CD30, CD69, CD134 (OX40), CD137 (4-1BB), CD147, CDw150 (SLAM), CD152 (CTLA-4), CD153 (CD30L), CD40L (CD154), NKG2D, ICOS, HVEM, HLA Class II, PD-1, Fas (CD95), FasL expressed on T and/or NK cells, CD40, CD48, CD58, CD70, CD72, B7.1 (CD80), B7.2 (CD86), B7RP-1, B7H3,

PD-L1, PD-L2, CD134L, CD137L, ICOSL, LIGHT expressed on APC and/or tumor cells; (3) cell modulating molecules such as CD16, NKp30, NKp44, NKp46, NKp80, 2B4, KIR, LIR, CD94/NKG2A, CD94/NKG2C expressed on natural killer (NK) cells, interferon (IFN)-alpha, IFN-beta, IFN-gamma, interleukin (IL)-1, IL-2, IL-3, IL-4, IL-6, IL-7, IL-8, IL-10, IL-11, IL-12, IL-15, CSFs (colony-stimulating factors), vitamin D3, IL-2 toxins, cyclosporin, FK-506, rapamycin, transforming growth factor (TGF)-beta, clotrimazole, nitrendipine, and charybdotoxin, accessory molecules such as lymphocyte function associated molecule (LFA)-1, CDlla/18, CD54 (intercellular adhesion molecule (ICAM)-1) CD106 (VCAM), and CD49a,b,c,d,e,f/CD29 (VLA-4); (4) adhesion molecules such as ICAM-1, ICAM-2, GlyCAM-1, CD34, anti-LFA-1, anti-CD44, anti-beta7, chemokines, CXCR4, CCR5, anti-selectin L, anti-selectin E, and anti-selectin P; (5) toxic molecules such as cyclophosphamide, methrotrexate, Azathioprine, mizoribine, 15-deoxuspergualin, neomycin, staurosporine, genestein, herbimycin A, Pseudomonas exotoxin A, saporin, Rituxan, Ricin, gemtuzumab ozogamicin, Shiga toxin, heavy metals like inorganic and organic mercurials, and FN18-CRM9, radioisotopes such as incorporated isotopes of iodide, cobalt, selenium, tritium, and phosphor, and haptens such as DNP, and digoxiginin; or (6) antibodies or antibody derivatives or fragments, or combinations of (1) - (5). The MHC molecule construct further comprises one or more labeling compounds that are attached to the carrier molecule, one or more of the binding entities or one or more of the MHC molecules. The labeling compound, which is directly or indirectly detectable, is a fluorescent label, an enzyme label, a radioisotope, a chemiluminescent label, a bioluminescent label, a polymer, a metal particle, a hapten, an antibody or a dye. It is selected from: (1) fluorescent labels such as 5-(and 6)-carboxyfluorescein, 5- or 6-carboxyfluorescein, 6-(fluorescein)-5-(and 6)-carboxamido hexanoic acid, fluorescein isothiocyanate (F)TC), rhodamine, tetramethylrhodamine, and dyes such as Cy2, Cy3 and Cy5, optionally substituted coumarin including AMCA, PerCP, phycobiliproteins including R-phycoerythrin (RPE) and allophycoerythrin (APC), Texas Red, Princeston Red, Green fluorescent protein (GFP) and their analogs, and conjugates of R-phycoerythrin or allophycoerythrin and e.g. Cy5 or Texas Red, and inorganic fluorescent labels based on semiconductor nanocrystals (like quantum dot and Qdot (RTM) nanocrystals), and time-resolved fluorescent labels based on lanthanides like Eu3+ and Sm3+; (2) haptens such as DNP, biotin, and digoxiginin; (3) enzymatic labels such as horse radish peroxidase (HRP), alkaline phosphatase (AP), betagalactosidase (GAL), glucose-6-phosphate dehydrogenase, beta-N-acetylglucosaminidase, beta-glucuronidase, invertase, Xanthine Oxidase, firefly luciferase and glucose oxidase (GO); (4) luminescence labels such as luminol, isoluminol, acridinium esters, 1,2-dioxetanes and pyridopyridazines; or (5) radioactivity labels such as incorporated isotopes of iodide, cobalt, selenium, tritium, and phosphor. The carrier molecule, which is soluble molecule, consists of: (1) polysaccharides including dextrans, carboxy methyl dextran, dextran polyaldehyde, carboxymethyl dextran lactone, and cyclodextrins, pullulans, schizophyllan, scleroglucan, xanthan, gellan, O-ethylamino guaran, chitins and chitosans including 6-0- carboxymethyl chitin and N-carboxymethyl chitosan; (2) derivatized cellolosics including carboxymethyl cellulose, carboxymethyl hydroxyethyl cellulose, hydroxy-ethyl cellulose, 6-amino-6-deoxy cellulose and O-ethyl-amine cellulose; (3) hydroxylated starch, hydroxypropyl starch, hydroxyethyl starch, carrageenans, alginates, and agarose, synthetic polysaccharides including ficoll and carboxy-methylated ficoll; (4) vinyl polymers including poly(acrylic acid), poly(acrylamides), poly(acrylic esters), poly(2-hydroxy ethyl meth-acrylate), poly(methyl methacrylate), poly(maleic acid), poly(maleic anhydride), poly(acrylamide), poly(ethyl-co-vinyl acetate), poly(methacrylic acid),

poly(vinyl-alcohol), poly(vinyl alcohol-co-vinyl chloroacetate), aminated poly(vinyl alcohol), and their co block polymers; (5) poly ethylene glycol (PEG) or polypropylene glycol or poly(ethylene oxide-co-propylene oxides) containing polymer backbones including linear, comb-shaped or StarBurst (RTM) dendrimers; (6) poly amino acids including polylysines, polyglutamic acid, polyurethanes, poly(ethylene imines), pluriol; (7) proteins including albumins, immunoglobulins, and virus-like proteins (VLP); or (8) polynucleotides, DNA, PNA, LNA, oligonucleotides or oligonucleotide dendrimer constructs. The MHC molecule is a vertebrate MHC molecule such as a human, murine, rat, porcine, bovine or avian molecule. Preferably the MHC molecule is a human MHC molecule. It is a peptide free MHC molecule. The MHC molecule comprises: (1) a MHC Class I molecule consisting of a heavy chain, a heavy chain combined with a beta2m, a heavy chain combined with a peptide or a heavy chain/beta2m dimer with a peptide; (2) a MHC Class II molecule consisting of an alpha/beta dimer, an alpha/beta dimer with a peptide, alpha/beta dimer combined through an affinity tag and an alpha/beta dimer combined through an affinity tag with a peptide; or (3) a MHC Class I like molecule or MHC Class II like molecule. Two of the MHC molecules or the peptides harbored by the MHC molecules are either the same or different. The MHC molecules are attached to the carrier molecule directly or via one or more binding entities. 1 - 2, 1 - 3, 1 - 4, 1 - 6, 1 - 8 or 1 - 10 MHC molecules are attached to the carrier molecule by each binding entity. The binding entity is selected from streptavidin (SA) and avidin or their derivatives, biotin, immunoglobulins, antibodies (monoclonal, polyclonal, and recombinant), antibody fragments and their derivatives, leucine zipper domain of AP-1 (jun and fos), hexa-his (metal chelate moiety), hexa-hat GST (glutathione S-tranferase) glutathione affinity, Calmodulin-binding peptide (CBP), Strep-tag, Cellulose Binding Domain, Maltose Binding Protein, S-Peptide Tag, Chitin Binding Tag, Immunoreactive Epitopes, Epitope Tags, E2Tag, HA Epitope Tag, Myc Epitope, FLAG Epitope, AU1 and AU5 Epitopes, Glu-Glu Epitope, KT3 Epitope, IRS Epitope, Btag Epitope, Protein Kinase-C Epitope, VSV Epitope, lectins that mediate binding to a diversity of compounds, including carbohydrates, lipids and proteins, e.g. Con A (Canavalia ensiformis) or WGA (wheat germ agglutinin) and tetranectin or Protein A or G (antibody affinity). Preferred Composition: The adjuvant of the composition is selected from saponins such as Quil A and Qs-21, oil in water emulsions such as MF59, MPL, PLG, PLGA, aluminium salts, calcium phosphate, water in oil emulsions such as IFA (Freund's incomplete adjuvant) and CFA (Freund's complete adjuvant), interleukins such as IL-1beta IL-2, IL-7, IL-12, and INFgamma, Adju-Phos (RTM), glucan, antigen formulation, biodegradable microparticles, Cholera Holotoxin, liposomes, DDE, DMEA, DMPC, DMPG, DOC/Alum Complex, ISCOMsr, muramyl dipeptide, monophosphoryl lipid A, muramyl tripeptide, and phospatidylethanolamine, preferably from saponins such as Quil A and Qs-21, MF59, MPL, PLG, PLGA, calcium phosphate, and aluminium salts. The excipient is selected from diluents, buffers, suspending agents, wetting agents, solubilizing agents, pH-adjusting agents, dispersing agents, preserving agents, and/or colorants. Preferred Method: Detecting the presence of MHC recognizing cells in a sample comprises: (a) providing a sample suspected of comprising MHC recognizing cells;(b) contacting the sample with a MHC molecule construct; and (c) determining any binding of the MEC molecule construct, the binding of which indicates the presence of MHC recognizing cells. Monitoring MHC recognizing cells or establishing a prognosis of a disease or diagnosing a disease, or determining the status of a disease, involving MHC recognizing cells comprises: (a) providing a sample suspected of comprising MHC recognizing cells;(b) contacting the sample with a MHC molecule construct; and (c) determining any binding of the MHC molecule construct. Determining the effectiveness of a medicament against a disease involving MHC recognizing

cells comprises: (a) providing a sample from a subject receiving treatment with a medicament; (b) contacting the sample with a MHC molecule construct; (c) determining any binding of the MHC molecule construct. The determination of the binding is carried out by inspection in a microscope, by light, by fluorescence, by electron transmission or by flow cytometry. The MHC recognizing cells are selected from subpopulations of CD3+ T-cells, gamma, delta T-cells, alpha, beta T-cells, CD4+ T-cells, T helper cells, CD8+ Tcells, Suppressor T-cells, CD8+ cytotoxic T-cells, cytotoxic T-cells (CTL)s, natural killer (NK) cells, NKT cells, LAK cells, and MAK. The MHC recognizing cells are involved in a disease of inflammatory, auto-immune, allergic, viral, cancerous, infectious, allo- or xenogene (graft versus host and host versus graft) origin. Obtaining MHC recognizing cells comprises: (a) bringing a sample from a subject comprising MHC recognizing cells into contact with a MHC molecule construct, where the MHC recognizing cells become bound to the MHC molecule construct; (b) isolating the bound MHC molecule construct and the MHC recognizing cells; and (c) expanding the MHC recognizing cells to a clinically relevant number. The isolation is carried out by applying a magnetic field or by flow cytometry. The MHC recognizing cells are liberated from the MHC molecule construct prior to expansion. The disease consists of chronic inflammatory bowel disease such as Crohn's disease or ulcerative colitis, sclerosis, type I diabetes, rheumatoid arthritis, psoriasis, atopic dermatitis, asthma, malignant melanoma, renal carcinoma, breast cancer, lung cancer, cancer of the uterus, cervical cancer, prostate cancer, brain cancer, head and neck cancer, leukemia, cutaneous lymphoma, hepatic carcinoma, colorectal cancer, bladder cancer, rejection-related disease, Graft-versus-host-related disease, or a viral disease associated with hepatitis, acquired immunodeficiency syndrome (AIDS), measles, pox, chicken pox, rubella or herpes. The sample is selected from histological material, cytological material, primary tumors, secondary organ metastasis, fine needle aspirates, spleen tissue, bone marrow specimens, cell smears, exfoliative cytological specimens, touch preparations, oral swabs, laryngeal swabs, vaginal swabs, bronchial lavage, gastric lavage, from the umbilical cord, and from body fluids such as blood (e.g. from a peripheral blood mononuclear cell (PBMC) population isolated from blood or from other blood-derived preparations such as leukopheresis products), from sputum samples, expectorates, and bronchial aspirates. The sample is mounted on a support. An adoptive cellular immunotherapeutic method, inducing energy of a cell, or up-regulating, down-regulating or modulating an immune response in, or treating an animal, including a human being comprises administering the therapeutic composition. Producing a therapeutic composition comprises: (a) providing the MHC molecule construct solubilizing or dispersing the MHC molecule construct in a medium suitable for therapeutic substances; and (b) optionally adding other adjuvants and/or excipients. The method also comprises: (a) obtaining MHC recognizing cells using the MHC molecule construct;(b) expanding such MHC recognizing cells to a clinically relevant number, (c) formulating the obtained cells in a medium suitable for administration; and (d) optionally adding adjuvants and/or excipients.

ACTIVITY - Cytostatic; Antiinflammatory; Dermatological; Antiasthmatic; Antidiabetic; Anti-HIV; Virucide; Antiarteriosclerotic; Antiulcer; Antirheumatic; Antiarthritic; Antipsoriatic; Immunosuppressive. No biological data is given.

MECHANISM OF ACTION - Gene therapy.

USE - The MHC molecule construct is useful as a therapeutic composition in in vivo or ex vivo therapy, for treating, preventing, stabilizing or alleviating a disease involving MHC recognizing cells, for monitoring MHC recognizing cells or establishing a prognosis of a disease or diagnosing a disease, or determining the status of a disease or the effectiveness of a medicament against a disease, involving MHC

recognizing cells, e.g., chronic inflammatory bowel disease such as Crohn's disease or ulcerative colitis, sclerosis, type I diabetes, rheumatoid arthritis, psoriasis, atopic dermatitis, asthma, malignant melanoma, renal carcinoma, breast cancer, lung cancer, cancer of the uterus, cervical cancer, prostate cancer, brain cancer, head and neck cancer, leukemia, cutaneous lymphoma, hepatic carcinoma, colorectal cancer, bladder cancer, rejection-related disease, Graft-versus-host-related disease, or a viral disease associated with hepatitis, Acquired Immunodeficiency Syndrome (AIDS), measles, pox, chicken pox, rubella or herpes. The MHC molecule construct is also useful for flow cytometric, histological or cytological method (all claimed.)

ADMINISTRATION - Administered via oral, rectal, nasal, topical or parenteral route, e.g., intravenous, intramuscular, intraarticular, subcutaneous, intradermal, epicutaneous/transdermal, and intraperitoneal, or by infusion (claimed). No specific dosage is given.

EXAMPLE - The preparations of SA conjugated dextrans of different molecular sizes were mixed with amounts of human leukocyte antigen (HLA) complexes corresponding to a ratio of two biotinylated HLA Class I molecules per SA molecule. The HLA molecule was added directly to a solution of SA-conjugated dextrans. Thus, MHC molecule constructs were formed. (304 pages)

L8 ANSWER 57 OF 71 BIOTECHDS COPYRIGHT 2008 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2002-12040 BIOTECHDS <<LOGINID::20080318>>
TITLE: Identifying inhibitor of bacterial tetrahydrofolate biosynthesis for treating bacterial infection, by contacting a cell having ketopantoate hydroxymethyltransferase promoter with an agent and measuring promoter activity;
vector-mediated gene transfer and expression in host cell for high throughput screening, drug screening and bacterium infection therapy 3-methyl-2-oxobutanoate-hydroxymethyltransferase
AUTHOR: MURPHY C
PATENT ASSIGNEE: MILLENNIUM PHARM INC
PATENT INFO: WO 2002014559 21 Feb 2002
APPLICATION INFO: WO 2000-US41665 11 Aug 2000
PRIORITY INFO: US 2000-224925 11 Aug 2000
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2002-269209 [31]
AN 2002-12040 BIOTECHDS <<LOGINID::20080318>>
AB DERWENT ABSTRACT:

NOVELTY - Determining (M) whether a test compound (C) is an inhibitor of bacterial tetrahydrofolate (THF) biosynthesis, comprising contacting a bacterial cell with (C), where the cell contains a promoter, the activity of which is increased in the presence of a compound that inhibits THF biosynthesis, and measuring activity of the promoter, is new.

DETAILED DESCRIPTION - (M) involves contacting a bacterial cell with (C), where the cell contains a promoter, whose activity is increased in the presence of a compound that inhibits THF biosynthesis, and measuring activity of the promoter, where an increase in the activity, relative to the activity of the promoter in the absence of (C), indicates that (C) is an inhibitor of THF biosynthesis. INDEPENDENT CLAIMS are also included for the following: (1) a composition (C1) comprising an antibacterial agent identified by M; (2) an inhibitor (I) of bacterial tetrahydrofolate biosynthesis prepared by using C1 as a lead compound; (3) an antibacterial agent prepared by using C1 as a lead compound; and (4) a composition (C2) comprising the above antibacterial agent.

BIOTECHNOLOGY - Preferred Method: The promoter is ketopantoate hydroxymethyltransferase (panB) promoter which comprises nucleotides

13043-13536 in the GenBank entry Accession No.L47709, or its fragment. The cell contains the promoter operably linked to a reporter gene such as beta-galactosidase (lacZ), chloramphenicol acetyltransferase (cat), beta-glucuronidase (gus), a luciferase gene, and a green fluorescent protein gene. The activity of the promoter is measured by: an antibody specific for aspartate 1-decarboxylase, pantothenate synthase or ketopantoate hydroxymethyltransferase; an assay for the activity of the above enzymes; by detecting the RNA species transcribed from the gene regulated by the promoter; or by measuring binding of antibodies to a product of the reporter gene.

ACTIVITY - Antibacterial. No suitable data given.

MECHANISM OF ACTION - Inhibitor of bacterial THF biosynthesis; inhibitor of bacterial growth.

USE - (M) is useful for determining whether a test compound is an inhibitor of bacterial THF biosynthesis, and also for determining whether a test compound is an antibacterial agent. The method comprises identifying an inhibitor of THF biosynthesis and determining whether the inhibitor inhibits growth of a bacterium. The inhibition of THF biosynthesis is detected as inhibition of para-aminobenzoic acid (PABA) uptake into cells and the inhibition is measured in a biochemical assay with a cell extract for an enzyme activity which is required for THF biosynthesis. The enzyme activity assayed is GTP cyclohydrase, 7,8 dihydroneopterin aldolase, 6-hydroxymethyl-7,8-dihydropterin pyrophosphokinase, dihydropteroate synthase, aminodeoxychorismate synthase, aminodeoxychorismate lyase, dihydrofolate:foly-polyglutamate synthase or dihydrofolate reductase. C1 is useful for treating a bacterial infection caused by Streptococcus pneumoniae, S.pyogenes, S.agalactiae, S.endocarditis, S.faecium, S.sangus, S.viridans, S.hemolyticus in a mammal, in particular a human. The bacterium is a pathogenic or non-pathogenic bacterium. The inhibitor identified by (M) is useful as a lead compound for preparing antibacterial agents. The method comprises screening multiple test compounds by (M), identifying candidate compounds that increase promoter activity, identifying and selecting from the candidate compounds a lead compound that inhibits growth of a bacterium, and formulating the selected compound as an antibacterial agent. The method optionally comprises derivatizing the selected lead compound to produce derivatives of lead compound, identifying a derivative that inhibits growth of a bacterium and formulating the identified derivative as an antibacterial agent. (I) is useful for inhibiting bacterial THF biosynthesis in bacteria infecting an organism. C2 is useful for inhibiting growth of bacteria in an organism having a bacterial infection (claimed). The compounds can be used to treat infection of gram negative bacteria e.g., Shigella, Escherichia coli, Klebsiella, and Yersinia.

ADMINISTRATION - Administered topically, orally, nasally, buccally, subcutaneously, or intraperitoneally, at a dosage of 1-100 mg/kg of body weight.

ADVANTAGE - (M) is rapid and convenient and can be used for high-throughput screening of a wide variety of test compounds. Lead compounds can readily be selected from a large number of test compounds. Assays employing the panB promoter are capable of detecting THF biosynthesis inhibitors at concentrations both above and below their minimal inhibitory concentrations. The assays are cell-based and can be used to identify antibacterial agents that can efficiently enter bacterial cells. As THF is the product of the multi-step biochemical pathway, (M) enables the identification of compounds that may inhibit any enzymatic function or step in the pathway.

EXAMPLE - An assay was performed to identify inhibitors of

tetrahydrofolate biosynthesis. The bacterial strain PY79 (amy::PpanB::lacZ, cat), containing the ketopantoate hydroxymethyltransferase (panB) promoter operably linked to the coding sequence of a lacZ reporter gene, the silent chromosome locus (amy) and a chloramphenicol acetyl transferase (cat) gene was used in the initial screen for inhibitors of tetrahydrofolate biosynthesis. A bacterial glycerol stock was prepared. To prepare cells for use in the assay of test compounds, 5 microl of the glycerol stock was diluted in 80 ml of low salt Luria-Bertani (LB) medium. A 15 microl aliquot of this diluted glycerol stock was then added to 900ml of low salt LB medium and grown to an optical density of 0.6 using 600nm wavelength in a shaking incubator at 30degreesC. Chemical libraries containing test compounds at 10 mg/ml in dimethylsulfoxide (DMSO) were diluted to 100 microg/ml with 50 mM HEPES (4-(2-hydroxyethyl)-1-piperazine- ethanesulfonic acid) buffer (pH 7.4). The test compounds (e.g., 0.1 microg or 0.05 microg) were dispensed into each well of a microplate (e.g., a 96 or 384-well microplate). The dispensed compounds were dried on the plates. A 50 microl sample of the bacteria was added to each well of the microplate. Trimethoprim was used as a control in wells of the microplate lacking a test compound. Bacteria and test compounds (or trimethoprim control) were then incubated at 30degreesC for 5 hours. To assay for an increase in the activity of the panB promoter, an increase in expression of the lacZ reporter gene expression was measured. A 50 microl aliquot of 2X substrate buffer containing 0.4 ml of Galacton-Star substrate, 2 ml of Sapphire II luminescence signal enhancer and 7.6 ml of lysis buffer was added to each well of the plate. Chemiluminescence was measured. A chemiluminescent signal that was at least 3 times the standard deviation, plus the mean, indicated that the test compound was a lead or candidate compound, i.e., a compound that increased the activity of the promoter and was a tetrahydrofolate biosynthesis inhibitor. The trimethoprim controls produced a chemiluminescent signal that was at least equal to 4 times the mean. (31 pages)

L8 ANSWER 58 OF 71 BIOTECHDS COPYRIGHT 2008 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2002-10610 BIOTECHDS <<LOGINID::20080318>>
TITLE: Methods for detecting one or more non-nucleic acid analytes using fusion polypeptides with specificity for the analyte, where the polypeptide comprises first and second inactive functional domains and an analyte binding domain; enzyme electrode, biosensor, DNA array and high throughput screening, useful for diagnosis
AUTHOR: MINSHULL J; DAVIS S C; WELCH M; RAILLARD S A; VOGEL K; KREBBER C
PATENT ASSIGNEE: MAXYGEN INC
PATENT INFO: WO 2002010750 7 Feb 2002
APPLICATION INFO: WO 2000-US24182 31 Jul 2000
PRIORITY INFO: US 2000-244764 31 Oct 2000
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2002-206219 [26]
AN 2002-10610 BIOTECHDS <<LOGINID::20080318>>
AB DERWENT ABSTRACT:
NOVELTY - Methods for detecting one or more non-nucleic acid analyte (NAA) using fusion polypeptides with specificity for the analyte, where the polypeptide comprises a first inactive functional domain, an analyte binding domain and a second inactive functional domain, are new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following: (1) a method (M1) for detecting one or more NAA, comprising: (a) providing at least one fusion polypeptide (P1) with specificity for a NAA, where P1 comprises a first inactive functional

domain, an analyte binding domain, and a second inactive functional domain, where binding of the NAA results in a conformational change which brings the first inactive functional domain and the second inactive functional domain into proximity, therefore converting the first and second inactive functional domains into an optically detectable functional domain; (b) contacting P1 with a sample comprising the NAA; and (c) detecting the conformational change induced by binding of the NAA, where the NAA is selected from a small organic molecule, a peptide, a polypeptide and a dissolved gas; (2) another method (M2) for detecting one or more NAA, comprising: (a) step (a) of M1, where the first and second inactive functional domains are converted into a catalytic functional domain; (b) providing a substrate for the catalytic functional domain; (c) contacting the fusion polypeptide with a sample comprising the analyte; and (d) detecting the conversion of the substrate to a product; (3) another method (M3) for detecting one or more NAA, comprising: (a) providing at least one polypeptide with specificity for a NAA, where the polypeptide comprises an analyte binding domain and a catalytic domain, where binding of the analyte results in an allosteric conformational change which activates the catalytic domain resulting in conversion of a substrate to a detectable product; and (b) providing a substrate for the catalytic domain; (c) contacting the polypeptide with a sample comprising the analyte; and (d) detecting the product produced by activity of the catalytic domain on the substrate; (4) a method (M4) for detecting an analyte, comprising providing at least one biopolymer which undergoes a conformational change upon binding to an analyte, contacting a sample comprising the analyte to the biopolymer; and detecting the conformation change induced by binding of the analyte, where the analyte is not an ion; (5) a method (M5) for identifying a physiologic state, comprising providing at least one biopolymer which biopolymer undergoes a conformational change upon binding to a marker associated with a physiologic state, contacting the biopolymer with a biological sample comprising the marker, and detecting the conformation change induced by binding of the marker, thereby identifying the physiologic state associated with the marker; (6) a biosensor comprising: (a) a support; and (b) at least one polypeptide with specificity for a NAA, where the polypeptide comprises an analyte binding domain and a catalytic domain, where binding of the analyte results in an allosteric conformational change which activates the catalytic domain resulting in conversion of a substrate to a detectable product, where the polypeptide is immobilized on the support; or (c) at least one fusion polypeptide with specificity for a NAA, where the polypeptide comprises a first inactive functional domain, and analyte binding domain, and a second inactive functional domain, where binding of the analyte brings the first inactive functional domain and the second inactive functional domain into proximity, thereby converting the first and second inactive functional domains into a functional catalytic or optically detectable domain where the fusion polypeptide is immobilized on the support; or (d) a polypeptides immobilized on the solid support, where the polypeptides having different analyte binding specificities, and a detection system; (7) a method (M6) of sensing one or more test stimulus, comprising: (a) providing a library of biopolymers comprising nucleic acid variants or expression products of the nucleic acid variants; (b) arraying the library in a spatial or logical format to provide a physical or logical array; (c) contacting one or more calibrating stimulus to the array, where one or more members of the array produce one or more detectable signals in response to contact by the one or more calibrating stimulus, thereby producing a calibrating array pattern which identifies contact of the array by the one or more calibrating stimulus; (d) contacting at least one test stimulus to the array, thereby producing a test stimulus array pattern; and (e) comparing the test stimulus array

pattern to the calibrating array pattern, thereby identifying the test stimulus; (8) a method (M7) of using a re-usable array of biopolymers, comprising: (a) providing a physical or logical array of biopolymers comprising nucleic acid variants or expression products of the nucleic acid variants; (b) contacting the physical or logical array with one or more first stimulus; (c) observing a first resulting response of the array, or collecting a first product resulting from contact between the array and the first stimulus; (d) reusing the array by contacting the array a second time with the first stimulus, or with a second stimulus, and observing a second resulting response of the array, or collecting a second product resulting from contact between the array and the first or second stimulus, and, optionally, comparing the first resulting response of the array to the second resulting response of the array; (9) biopolymer array produced by M6 or M7; and (10) a computer comprising a data set corresponding to the labeling biopolymer sensor array pattern or test biopolymer sensor array pattern of M6 or M7.

BIOTECHNOLOGY - Preferred Method: In M1, the first and second inactive functional domains are derived from a green fluorescent protein or a green fluorescent protein homologue. M1 comprises detecting an electrochemical signal produced by binding of the analyte or detecting an optical signal produced by binding of the analyte. The optical signal is detected by one or more of: ultraviolet spectrophotometry, visible light spectrophotometry, surface plasmon resonance; calorimetry, fluorescence polarization; fluorescence quenching; colorimetric quenching; fluorescence wavelength shift; fluorescence resonance energy transfer (FRET); enzyme linked immunosorbent assay (ELISA) or liquid crystal displays (LCD). The optical signal is produced by displacement of a tethered substrate upon binding of the analyte. The tethered substrate is an analyte analogue. In M2, the conversion of the substrate to a product is detected by detecting an electrochemical signal or an optical signal which is detected as described above. M1, M2, M3, M4 and M5 comprise providing a physical or logical array comprising polypeptides which have different analyte binding specificities. In M1, M2, M4 and M5, the polypeptides provide a common signal. The NAA comprises a small molecule, a hormone or a metabolite. The sample is a biological sample (blood, plasma, urine, sweat, cerebrospinal fluid and tears) or an environmental sample. In M3, the conversion of the substrate to product produces an electrochemical signal or an optical signal which is detected as described above. In M3, the conversion of substrate to product by the analyte-bound polypeptides is detected by detecting a common signal. The sample is a biological sample, an environmental sample, or an industrial sample. The sample further comprises an agonist or an antagonist. The analyte comprises a small molecule, a hormone, a metabolite, an ion, an antigen or a ligand. In M4, the biopolymer comprises a polypeptide which comprises an antibody or a receptor. The conformation change results in generation of an optical signal which is detected as described above. The optical signal is produced by displacement of a tethered substrate upon binding of the analyte. The tethered substrate is an analyte analogue. In M5, the biopolymer comprises a polypeptide which comprises an enzyme, an antibody, a receptor or a fusion protein. Preferably the polypeptide is P1, where binding of the analyte results in a conformational change which brings the first inactive functional domain and the second inactive functional domain into proximity, thereby converting the first and second inactive functional domains into a functional catalytic or fluorescent domain. The conformation change results in generation of an optical signal which is detected as described above. The optical signal is produced by displacement of a tethered substrate upon binding of the analyte. The tethered substrate is an analyte analogue. In M6 and M7, the

biopolymer library comprises or is encoded by recursively recombined nucleic acids. The biopolymer library comprises or is encoded by artificially mutated or artificially shuffled nucleic acids. Alternatively, the biopolymer library comprises or is encoded by species variants of one or more nucleic acids. Alternatively, the biopolymer library comprises or is encoded by nucleic acids produced by recursive recombination of species variants of one or more nucleic acids. The biopolymer library comprises photoactivatable members. The method comprises masking a portion of the array and exposing the resulting masked array to light. The array comprises one or more of a conductive member, a capacitive member, an optically responsive member, an electrically responsive member, and an electrically or logically gated or gateable member. Alternatively, the array comprises one or more of: a bio-laser, a polychromic display, a molecular poster, a bar code, a protein TV, a molecular camera, a UV (ultra-violet) molecular camera, an IR (infra-red) molecular camera, or a flat screen display. The array members comprise one or more proteins. The proteins comprise electrically conductive proteins. The proteins are purified. The proteins comprise one or more purification tags such as His tags, and FLAG tags. Arraying the biopolymer library comprises: (a) arranging the members of the library in a logically accessible format; (b) arranging the members of the library in a physically grided format; (c) plating the members of the library in microtiter trays; or (d) arranging the members of the library for parallel examination. Arraying the biopolymer library or expression product library comprises recording the position of members of the library in one or more database, or arranging the members of the library for sequential examination. The first, second, test or calibrating stimulus are simultaneously, sequentially or alone contacted to biopolymer library members. Contact of the of first, second, test or calibrating stimulus produces a signature for a sample type. The signature is representative of one or more phenomenon selected from a metabolic state of a cell, an operon induction in or by a cell, an induction of cell growth, a proliferation in or caused by a cell, a cancer of a cell or tissue, or organism, apoptosis, cell death, cell cycle, cell or tissue differentiation, tumorigenesis, disease state, drug resistance, drug efficacy, antibiotic spectrum, drug toxicity, gas level, SOx, NOx Alzheimer's disease, infection, presence of viruses, viral infection, bacterial infection, HIV infection, AIDS, serum cholesterol, CHDL (undefined) level, LDL (low density lipoprotein), serum triglyceride level, blood glucose level, ion or gas production or internalization, cytokine receptor expression, antibody-antigen interactions, pregnancy, fertility, fecundity, presence or absence of narcotics or other controlled substances, heart attack, presence or absence of steroids, body temperature, presence of sound waves, taste, scent, food composition, beverage composition, and an environmentally monitored condition. The first, second, test or calibrating stimulus are contacted to library members in a microtiter plate or fixed on a solid substrate. Alternatively, the first, second, test or calibrating stimulus are contacted to library members, or their expression products, fixed on a solid substrate, where the solid substrate comprises a Nickel-NTA coated surface, a silane-treated surface, a pegylated surface, or a treated surface. The biopolymer library members or expression products thereof are fixed to an organizational matrix in spatially addressable locations. Alternatively, the first, second, test or calibrating stimulus are contacted to biopolymer library members, where member types are fixed on the surface of one or more beads. One or more beads each comprise more than one detectable feature. More than one detectable feature includes a first feature which identifies binding by the first, second, test or calibrating stimulus and a second feature which identifies either the type of bead or the type of library member or expression product thereof which is bound to the bead. The first stimulus, the second stimulus, the

calibrating stimulus or the test stimulus, is selected from light, radiation, an atom, an ion, and a molecule. The first, second, test or calibrating stimulus comprises, hybridizes to, binds, acts upon or is acted upon by one or more of: radiation, a polymer, a chemical group, a biopolymer, a nucleic acid, an RNA, a DNA, a protein, a ligand, an enzyme, a chemo-specific enzyme, a regio-specific enzyme, a stereo-specific enzyme, a nuclease, a restriction enzyme, an restriction enzyme which recognizes a triplet repeat, a restriction enzyme that recognizes DNA superstructure, a restriction enzyme with an 8 base recognition sequence, an enzyme substrate, a regio-specific enzyme substrate, a stereo-specific enzyme substrate, a ligase, a thermostable ligase, a polymerase, a thermostable polymerase, a co-factor, a lipase, a protease, a glycosidase, a toxin, a contaminant, a metal, a heavy metal, an immunogen, an antibody, a disease marker, a cell, a tumor cell, a tissue-type, cerebrospinal fluid, a cytokine, a receptor, a chemical agent, a biological agent, a fragrance, a pheromone, a hormone, an olfactory protein, a metabolite, a molecular camera protein, a rod protein, a cone protein, a light-sensitive protein, a lipid, a pegylated material, an adhesion amplifier, a drug, a potential drug, a lead compound, a protein allele, an oxidase, a reductase, or a catalyst. The first, second, test or calibrating stimulus are contacted to the members of the library by incubating a solution comprising the test molecule or the calibrating molecule with the library members. The solution is a fluid, a polymer solution or a gel. Comparison of the test array pattern and the calibrating array pattern, or of the first resulting response of the array and the second resulting response of the array, is performed by a computer. The first, second, test or calibrating stimuli are contacted to the array to produce resulting array patterns. The methods further comprise recording the resulting array patterns in one or more databases, and assigning a bar code to each resulting array pattern. The test array pattern, the calibrating array pattern, the first resulting response of the array, or the second resulting response of the array, comprises variations in the presence or absence of signal at different locations on or in the array. The test array pattern, the calibrating array pattern, the first resulting response of the array, or the second resulting response of the array comprises variations in the level of signal at different locations on the array. The test array pattern, the calibrating array pattern, the first resulting response of the array, or the second resulting response of the array comprises variations in the presence and intensity of signal at different locations on the array. An intensity of the test array pattern, the calibrating array pattern, the first resulting response of the array, or the second resulting response of the array comprises is measured to quantify the first, second, test or calibrating stimulus. The test array pattern, the calibrating array pattern, the first resulting response of the array, or the second resulting response of the array comprises one or more fluorophore emission, photon emission, chemiluminescent emission, coupled luminescent/fluorescent emission or quenching, or detection of one or more fluorophore emission. The test array pattern, the calibrating array pattern, the first resulting response of the array, or the second resulting response of the array comprises an electrochemically detectable signal, an amperometrically detectable signal, a potentiometrically detectable signal, a signal detectable as a change in pH, a signal based on specific ion levels, a signal based on changes in conductivity, a pizoelectric signal, a change in resonance frequency, a signal detectable as surface accoustic waves, or a signal detectable by quartz crystal microbalances. The test array pattern, the calibrating array pattern, the first resulting response of the array or the second resulting response of the

array comprises multiple wavelengths of light. The test array pattern, the calibrating array pattern, the first resulting response of the array or the second resulting response of the array is generated by detection of one or more of: light, H2O2, glucose oxidase, NADP, NADPH+, NAD(P)H reductase, a change in reduction potential, a change in protein conformation, a change in intrinsic fluorescence, fluorescence, luminescence, FRET, absorption, surface plasmon resonance, antigen binding, antibody binding, enzyme activity, opening of an ion channel, or label binding. At least one member of the biopolymer library, or an expression product thereof, is selected, prior to the arraying step, for one or more of: enhanced stability, orientation of protein binding, improved production, cost of manufacture, optimal activity of expressed members which comprise a tag, overexpression mutations, optimized protein folding, permanent enzyme secretion, improved operators, improved ribosome binding sites, avidity, selectivity, production of a detectable side product, and detection limit. The test array pattern, the calibrating array pattern, the first resulting response of the array or the second resulting response of the array are detected by one or more of: a microscope, a CCD, a phototube, a photodiode, an LCD (liquid crystal display), a scintillation counter, film, or visual inspection. The test array pattern, the calibrating array pattern, the first resulting response of the array or the second resulting response of the array are digitized and stored in one or more database in one or more computer. M6 and M7 further comprise contacting at least one additional stimulus to the array, and comparing a resulting additional test stimulus array pattern to the calibrating array pattern, thereby identifying the at least one additional stimulus, or observing an additional resulting response of the array, or collecting an additional product resulting from contact between the array and the additional or a previous stimulus, and optionally comparing the additional resulting response to any one or more previous responses of the array. The method comprises contacting the array with 2, preferably 10, or more additional stimuli. Preferred Biosensor: The biosensor further comprising a conductive element or an optically detectable element. The polypeptides are immobilized with an immobilization matrix selected from carbon paste and a non-biological polymeric matrix. The biosensor further comprises a display. Preferred Biopolymer Array: The biopolymer array is stable for at least one year under pre-selected storage conditions.

USE - The methods and biosensors are useful for detecting a wide range of biological, chemical and biochemical stimuli, e.g. polypeptides, hormones, metabolite and small molecules. They are useful in medical, environmental and industrial diagnostic procedures, for e.g. the array can be used for detection of protein biomarkers associated with disease or other physiological condition.

EXAMPLE - Regardless of the format of the library array, calibration and standardization is performed by exposing the array components to one or more known standard, e.g., calibrating or pattern forming, stimulus. For example, to standardize and calibrate the array for detection of small organic molecules, the array is contacted with known organic molecules, e.g., phenol, toluene, xylenol, and selected derivatives. The resulting response, e.g., luciferase or GFP (green fluorescent protein) activity, or calibrating array pattern, is detected and recorded, for example, by a CCD camera or other photoelectric device. The array is then exposed to one or more test stimulus. In the case of cultures, this can be accomplished by exposing replicate cultures to one or more test compounds, while in the case of proteins arrayed on a chip, this is best accomplished by washing under conditions amenable to preservation of the array, followed by subsequent exposure to the test compounds. Alternative formats for performing detection assays, e.g., on microfluidic devices (e.g.,

LabMicrofluidic device (RTM) high throughput screening system (HTS) by Caliper Technologies, Mountain View, CA or the HP/Agilent technologies Bioanalyzer using LabChip (TM) technology by Caliper Technologies Corp. See, also, www.calipertech.com) are available and favorably employed in the context of the present invention.(159 pages)

L8 ANSWER 59 OF 71 BIOTECHDS COPYRIGHT 2008 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2002-08394 BIOTECHDS <<LOGINID::20080318>>
TITLE: Identifying nucleic acid encoding divalent cation transporters comprises exposing host cell with mitochondrion having cation-sensitive indicator contacted with construct encoding transporter to cation and detecting signal; vector-mediated gene transfer and expression in yeast host cell for recombinant protein production
AUTHOR: PFEIFFER D R; MURPHY A N; JUNG D W; BRADSHAW P C
PATENT ASSIGNEE: MITOKOR; UNIV OHIO STATE RES FOUND
PATENT INFO: WO 2002002816 10 Jan 2002
APPLICATION INFO: WO 2000-US20750 29 Jun 2000
PRIORITY INFO: US 2000-215737 29 Jun 2000
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2002-154762 [20]
AN 2002-08394 BIOTECHDS <<LOGINID::20080318>>
AB DERWENT ABSTRACT:

NOVELTY - Identifying (M1) a nucleic acid molecule encoding a mitochondrial divalent cation transporter (I), is new.

DETAILED DESCRIPTION - Identifying (M1) a nucleic acid molecule encoding a mitochondrial divalent cation transporter (I) comprising: (a) contacting a biological sample comprising a host cell (HC) comprising a mitochondrion which has a divalent cation (DC)-sensitive indicator molecule (IM) that is capable of generating a detectable signal in the presence of a DC, with a nucleic acid expression construct (EC) which comprises a promoter operably linked to a nucleic acid encoding a candidate (I), under suitable conditions to permit expression of (I); (b) exposing HC to DC under suitable conditions to permit transport of DC across a membrane by (I); and (c) detecting a signal generated by IM in a mitochondrion, and identifying a nucleic acid encoding (I), is new. An INDEPENDENT CLAIM is also included for preparation of (I) by culturing a HC comprising nucleic acid expression construct that encodes a protein comprising a candidate (I) identified by M1, under conditions to permit expression of the polypeptide and recovering the polypeptide.

WIDER DISCLOSURE - Also disclosed are: (1) EC encoding mitochondrial, calcium uniporter polypeptide; (2) screening such polypeptides expressed in suitable HC; (3) variants of EC; (4) sequences which hybridize to nucleic acid sequences encoding (I);(5) (I) encoded by EC; (6) fragment, derivative or analog of (I); (7) vectors comprising EC; and (8) HC comprising EC.

BIOTECHNOLOGY - Preferred Method: In M1, the DC is from barium, calcium, cobalt, iron, lanthanide series member, lead, magnesium, manganese, zinc and strontium, and HC is preferably prokaryotic or eukaryotic cell which is a yeast cell, which has a mitochondrion that lacks an endogenous electrogenic DC transporter, where the activity of at least one endogenous gene product which is preferably from electrogenic DC transporter and an electroneutral DC transporter, is substantially impaired. The nucleic acid expression construct further comprises at least an additional polynucleotide that regulates transcription preferably encoding a repressor of the regulated promoter, and the construct preferably encodes a candidate (I) that is expressed as a fusion protein with a polypeptide product of a second polynucleotide, where the fusion protein localizes to a cellular membrane which is from mitochondrial, vacuolar, vesicular, endoplasmic reticulum, Golgi,

chloroplast, and a plasma membrane, more preferably inner mitochondrial membrane. IM is preferably from aequorin protein, luciferase, a green fluorescent protein or their variants, 45Ca, rhod-2, fura-2, Indo-1, Fluo-3 and a FLASH sequence. In M1, HC comprises at least a second expression construct which directs expression of an esterase (comprising a mitochondrial targeting sequence) that localize to a mitochondrion, where the esterase is capable of cleaving IM precursor which is capable of crossing a cellular membrane, to provide IM, and where the signal generated by IM is detected by spectrophotometry, radiometry, fluorimetry, fluorescence resonance energy transfer (FRET) and flow cytofluorimetry. Preferably in M1, HC growth is impaired in the presence of Ca2+, where HC comprises a mutated ATPase gene, vacuolar assembly mutation or is a yeast PMC1/PMR1 double ATPase mutant, and the cell growth is detected by microscopy, enzyme activity, spectrophotometry, flow cytometry, fluorimetry or luminometry where DC is calcium at a concentration of 0.01-100 micro M.

USE - (M1) is useful for identifying a nucleic acid molecule encoding (I) (claimed).

EXAMPLE - The mitochondrial-targeting apoaequorin expression vector for mammalian cells, mtAEQ/pMT2, developed by Tizzuto et al was obtained. The cDNA insert was subcloned into the multiple cloning site of the pYES2 yeast expression vector using EcoR1. The pYES2 plasmid containing the Ga11 portion of the Ga11/Ga110 promoter region from Saccharomyces cerevisiae for inducible expression, and also contained the URA3 gene for selection. Vector propagation was performed by transformation into competent Escherichia coli cells. The ampicillin-resistant transformants were grown and the plasmids were purified and the orientation and insert number were checked. Another plasmid, designated ymtAeq/pGK, was also constructed, which directed the expression of a mitochondrially targeted aequorin fusion protein using a yeast mitochondrial cytochrome c oxidase subunit IV (COX IV) mitochondrial targeting polypeptide region instead of the human cytochrome c oxidase subunit VIII N-terminal targeting region that was used in the pYES2 construct. Aequorin-encoding cDNA, lacking the human mitochondrial targeting sequence and including the first twelve amino acids of the yeast mitochondrial targeting polypeptide, was amplified by polymerase chain reaction (PCR) using the pYES2 mitochondrially targeted aequorin construct as template and the following oligonucleotide primers. Forward oligo: 5'-AAAAGATCTAAAAATGCTTTCACTACGTCAATCTATAAGATTTTTCAAGCT TACATCAGACTTCGACAACCC-3', and reverse oligo: 3'-AAAGGTACCTTAGGGGACAGCTCCACCGT-3'. The PCR product was then cloned into the pGK yeast expression vector obtained using the Bg1 II and Asp 718 cloning sites in the pGK vector, and was then transformed into yeast strain INVSc1, and INVSc1 cells were transformed with the pGK plasmid encoding the yeast mitochondrially targeted apoaequorin fragment. Selection was carried out and transformed colonies were cultured and lysed and then treated with 0.12% Triton X-100 to release apoaequorin from the mitochondria. The supernatants were incubated with coelenterazine (2.5 micro M) and 2-mercaptoethanol (2 micro liter), to form the luminescent aequorin from its apoprotein. A transformant which yielded high luminescence was selected, precultured and spheroplasts were prepared using zymolyase. Apoaequorin in the intact or disrupted mitochondria was reconstituted by incubation with coelenterazine. The ratio of observed luminescence (L) to the potential luminescence remaining (Lmax) was calculated, and compared to a calibration curve which related this ratio to the free Ca2+ concentration. Thus, complete calibrated progress curves were generated. (133 pages)

ACCESSION NUMBER: 2002:35217421 BIOTECHNO <<LOGINID::20080318>>
TITLE: Advances in in vivo bioluminescence imaging of gene expression
AUTHOR: Contag C.H.; Bachmann M.H.
CORPORATE SOURCE: C.H. Contag, Department of Pediatrics, Stanford Univ. School of Medicine, Stanford, CA 94305-5208, United States.
E-mail: ccontag@cmgm.stanford.edu
SOURCE: Annual Review of Biomedical Engineering, (2002), 4/- (235-260), 146 reference(s)
CODEN: ARBEF7 ISSN: 1523-9829
DOCUMENT TYPE: Journal; General Review
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2002:35217421 BIOTECHNO <<LOGINID::20080318>>
AB To advance our understanding of biological processes as they occur in living animals, imaging strategies have been developed and refined that reveal cellular and molecular features of biology and disease in real time. One rapid and accessible technology for in vivo analysis employs internal biological sources of light emitted from luminescent enzymes, luciferases, to label genes and cells. Combining this reporter system with the new generation of charge coupled device (CCD) cameras that detect the light transmitted through the animal's tissues has opened the door to sensitive in vivo measurements of mammalian gene expression in living animals. Here, we review the development and application of this imaging strategy, in vivo bioluminescence imaging (BLI), together with in vivo fluorescence imaging methods, which has enabled the real-time study of immune cell trafficking, of various genetic regulatory elements in transgenic mice, and of in vivo gene transfer. BLI has been combined with fluorescence methods that together offer access to in vivo measurements that were not previously available. Such studies will greatly facilitate the functional analysis of a wide range of genes for their roles in health and disease.

L8 ANSWER 61 OF 71 BIOTECHNO COPYRIGHT 2008 Elsevier Science B.V. on STN DUPLICATE
ACCESSION NUMBER: 2002:34214365 BIOTECHNO <<LOGINID::20080318>>
TITLE: Stains, labels and detection strategies for nucleic acids assays
AUTHOR: Kricka L.J.
CORPORATE SOURCE: Dr. L.J. Kricka, Department of Pathology, University of Pennsylvania, Philadelphia, PA 19104, United States.
E-mail: kricka@mail.med.upenn.edu
SOURCE: Annals of Clinical Biochemistry, (2002), 39/2 (114-129), 165 reference(s)
CODEN: ACBOBU ISSN: 0004-5632
DOCUMENT TYPE: Journal; General Review
COUNTRY: United Kingdom
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2002:34214365 BIOTECHNO <<LOGINID::20080318>>
AB Selected developments and trends in stains, labels and strategies for detecting and measuring nucleic acids (DNA, RNA) and related molecules [e.g. oligo(deoxy)-nucleotides, nucleic acid fragments and polymerase chain reaction products] are surveyed based on the literature in the final decade of the 20th century (1991-2000). During this period, important families of cyanine dyes were developed for sensitive detection of double-stranded DNA, single-stranded

DNA, and oligo(deoxy)nucleotides in gels and in solution, and families of energy transfer primers were produced for DNA sequencing applications. The continuing quest for improved labels for hybridization assays has produced a series of candidate labels including genes encoding enzymes, microparticles (e.g. quantum dots, nanocrystals, phosphors), and new examples of the fluorophore (e.g. cyanine dyes) and enzyme class of labels (e.g. firefly luciferase mutants). Label detection technologies for use in northern and southern blotting assays have focused on luminescent methods, particularly enhanced chemiluminescence for peroxidase labels and adamantyl 1,2-dioxetanes for alkaline phosphatase labels. Sets of labels have been selected to meet the demands of multicolour assays (e.g. four-colour sequencing and single nucleotide primer extension assays). Non-separation assay formats have emerged based on fluorescence polarization, fluorescence energy transfer (TaqMan.TM., molecular beacons) and channelling principles. Microanalytical devices (microchips), high-throughput simultaneous test arrays (microarrays, gene chips), capillary electrophoretic analysis and dipstick devices have presented new challenges and requirements for nucleic acid detection, and fluorescent methods currently dominate in many of these applications.

L8 ANSWER 62 OF 71 USPATFULL on STN
ACCESSION NUMBER: 2001:218199 USPATFULL <<LOGINID::20080318>>
TITLE: Method for the enhancement of luminescence intensity from a reaction between adenosine triphosphate (ATP) and a luciferase/luciferin reactant system
INVENTOR(S): DiCesare, Joseph L., Redding, CT, United States

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2001046687	A1	20011129	
APPLICATION INFO.:	US 2001-821301	A1	20010329	(9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-193519P	20000331 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: ST. ONGE STEWARD JOHNSTON & REENS, LLC, 986 BEDFORD STREET, STAMFORD, CT, 06905-5619
NUMBER OF CLAIMS: 4
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 6 Drawing Page(s)
LINE COUNT: 1428
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Disclosed herein is a method for significantly enhancing the luciferase activity in a chemiluminescence assay technique. The disclosed method involves the use of trehalose, a-D-glucopyranosyl-a-D-glucopyranoside, in a chemiluminescent reactant system. By adding trehalose up to its saturation solubility level, increases in emission intensity of from 25-100%, or greater, can be attained.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 63 OF 71 USPATFULL on STN
ACCESSION NUMBER: 2001:196805 USPATFULL <<LOGINID::20080318>>
TITLE: Nucleic acid detection
INVENTOR(S): Shultz, John William, Verona, WI, United States

Lewis, Martin K., Madison, WI, United States
Leippe, Donna, Middleton, WI, United States
Mandrekar, Michelle, Oregon, WI, United States
Kephart, Daniel, Cottage Grove, WI, United States
Rhodes, Richard Byron, Madison, WI, United States
Andrews, Christine Ann, Cottage Grove, WI, United States
Hartnett, James Robert, Madison, WI, United States
Gu, Trent, Madison, WI, United States
Olson, Ryan J., Middleton, WI, United States
Welch, Roy, Palo Alto, CA, United States

PATENT ASSIGNEE(S): Promega Corporation, Madison, WI, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6312902	B1	20011106
APPLICATION INFO.:	US 1999-406065		19990927 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1999-358972, filed on 21 Jul 1999 Continuation-in-part of Ser. No. US 1999-252436, filed on 18 Feb 1999 Continuation-in-part of Ser. No. US 1998-42287, filed on 13 Mar 1998

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Fredman, Jeffrey
ASSISTANT EXAMINER: Chakrabarti, Arun
LEGAL REPRESENTATIVE: Welsh & Katz, Ltd.
NUMBER OF CLAIMS: 48
EXEMPLARY CLAIM: 1
LINE COUNT: 3389
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Processes are disclosed using the depolymerization of a nucleic acid hybrid to qualitatively and quantitatively analyze for the presence of a predetermined nucleic acid. Applications of those processes include the detection of single nucleotide polymorphisms, identification of single base changes, speciation, determination of viral load, genotyping, medical marker diagnostics, and the like.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 64 OF 71 USPATFULL on STN
ACCESSION NUMBER: 2001:125747 USPATFULL <<LOGINID::20080318>>
TITLE: Exogenous nucleic acid detection
INVENTOR(S): Shultz, John William, Verona, WI, United States
Lewis, Martin K., Madison, WI, United States
Leippe, Donna, Middleton, WI, United States
Mandrekar, Michelle, Oregon, WI, United States
Kephart, Daniel, Cottage Grove, WI, United States
Rhodes, Richard Byron, Madison, WI, United States
Andrews, Christine Ann, Cottage Grove, WI, United States
Hartnett, James Robert, Madison, WI, United States
Gu, Trent, Madison, WI, United States
Olson, Ryan J., Middleton, WI, United States
Wood, Keith V., Madison, WI, United States
Welch, Roy, Palo Alto, CA, United States

PATENT ASSIGNEE(S): Promega Corporation, Madison, WI, United States (U.S. corporation)

	NUMBER	KIND	DATE

PATENT INFORMATION: US 6270974 B1 20010807
APPLICATION INFO.: US 1999-406147 19990927 (9)
RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1999-358972, filed on 21 Jul 1999 Continuation-in-part of Ser. No. US 1999-252436, filed on 18 Feb 1999 Continuation-in-part of Ser. No. US 1998-42287, filed on 13 Mar 1998
DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Fredman, Jeffrey
ASSISTANT EXAMINER: Chakrabarti, Arun
LEGAL REPRESENTATIVE: Welsh & Katz, Ltd.
NUMBER OF CLAIMS: 51
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT: 4273
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Processes are disclosed using the depolymerization of a nucleic acid hybrid to qualitatively and quantitatively analyze for the presence of a predetermined exogenous nucleic acid. Applications of those processes include the detection of single nucleotide polymorphisms, identification of single base changes, determination of viral load, genotyping, medical marker diagnostics, and the like.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 65 OF 71 USPATFULL on STN
ACCESSION NUMBER: 2000:91744 USPATFULL <<LOGINID::20080318>>
TITLE: Nucleic acid amplification with DNA-dependent RNA polymerase activity of RNA replicases
INVENTOR(S): Dimond, Randall L., Madison, WI, United States
Ekenberg, Steven J., Mt. Horeb, WI, United States
Hartnett, James R., Madison, WI, United States
Hudson, Geoffrey R., Madison, WI, United States
Mendoza, Leopoldo G., Conroe, TX, United States
Miller, Katharine M., Verona, WI, United States
Monahan, John E., Walpole, MA, United States
Jones, Christopher L., Madison, WI, United States
Maffitt, Mark A., Madison, WI, United States
Martinelli, Richard A., Brighton, MA, United States
Pahuski, Edward E., Marshall, WI, United States
Schumm, James W., Madison, WI, United States(4)
PATENT ASSIGNEE(S): Promega Corporation, Madison, WI, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6090589		20000718
APPLICATION INFO.:	US 1995-480041		19950606 (8)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1990-638508, filed on 31 Dec 1990
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Marschel, Ardin H.
ASSISTANT EXAMINER: Riley, Jezia
LEGAL REPRESENTATIVE: Foley & Lardner
NUMBER OF CLAIMS: 121
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 11 Drawing Figure(s); 10 Drawing Page(s)
LINE COUNT: 3838
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention entails methods, and kits for carrying them out,

based on the discovery that an RNA replicase, such as Qβ replicase, has DNA-dependent RNA polymerase ("DDRP") activity with nucleic acid segments, including DNA segments and DNA:RNA chimeric segments, which comprise a 2'-deoxyribonucleotide or an analog thereof and which have sequences of RNAs that are autocatalytically replicatable by the replicase. The discovery of this DDRP activity provides methods of the invention for nucleic acid amplification wherein a nucleic acid, with a DNA segment with the sequence of an RNA that is autocatalytically replicatable by an RNA replicase, is provided as a substrate for the replicase. Assays of the invention include those wherein a nucleic acid analyte is hybridized with one or more nucleic acid probes, which include or are processed to generate a DNA segment which is amplifiable through production from the segment, catalyzed by the DDRP activity of an RNA replicase, of an autocatalytically replicatable RNA, which is autocatalytically replicated to provide an abundance of readily detectable reporter molecules.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 66 OF 71 USPATFULL on STN

ACCESSION NUMBER:	1999:155015 USPATFULL <<LOGINID::20080318>>
TITLE:	Methods of analysis/separation
INVENTOR(S):	Parton, Adrian, Exning, United Kingdom Huang, Ying, Houston, TX, United States Wang, Xiao-Bo, Houston, TX, United States Pethig, Ronald, Menia Bridge, United Kingdom MacGregor, Alastair R., Royston, United Kingdom Pollard-Knight, Denise V., St. Albans, United Kingdom
PATENT ASSIGNEE(S):	Scientific Generics Limited, Cambridge, United Kingdom (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5993631		19991130
APPLICATION INFO.:	US 1997-889459		19970708 (8)
RELATED APPLN. INFO.:	Division of Ser. No. US 1995-495447, filed on 20 Nov 1995, now patented, Pat. No. US 5653859		

	NUMBER	DATE
PRIORITY INFORMATION:	GB 1993-1122	19930121

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Beisner, William H.
ASSISTANT EXAMINER:	Starsiak, Jr., John S.
LEGAL REPRESENTATIVE:	Pillsbury Madison & Sutro LLP
NUMBER OF CLAIMS:	10
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	16 Drawing Figure(s); 12 Drawing Page(s)
LINE COUNT:	850

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Particles are subjected to travelling wave field migration (TWFM) to migrate the particles over an array of microelectrodes. Altered particles are produced by treating original particles in such a way so as to alter their TWFM characteristics and the altered TWFM characteristics are employed for analysis and/or separation of the altered particles. The particles may be cells, bacteria, viruses, biomolecules or plastics microspheres. They may be altered by binding to a ligand such as a metal microparticle via a selective linking moiety such as an antibody/antigen or oligonucleic acid, or be physical or chemical treatments.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 67 OF 71 USPATFULL on STN
ACCESSION NUMBER: 1998:150652 USPATFULL <<LOGINID::20080318>>
TITLE: Genetically engineered enzymes and their conjugates for diagnostic assays
INVENTOR(S): Brate, Elaine M, Grayslake, IL, United States
Brennan, Catherine A., Libertyville, IL, United States
Bridon, Dominique P., Morton Grove, IL, United States
Jaffe, Keeve D., Trevor, WI, United States
Krafft, Grant A., Glenview, IL, United States
Mandecki, Wlodzimierz, Libertyville, IL, United States
March, Steven C., Libertyville, IL, United States
Russell, John C., Greenfield, WI, United States
Yue, Vincent T., Deerfield, IL, United States
PATENT ASSIGNEE(S): Abbott Laboratories, Abbott Park, IL, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5843634		19981201
APPLICATION INFO.:	US 1996-657392		19960604 (8)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1993-100708, filed on 29 Jul 1993, now abandoned which is a continuation-in-part of Ser. No. US 1993-31165, filed on 9 Mar 1993, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Wax, Robert A.
ASSISTANT EXAMINER: Moore, William W.
LEGAL REPRESENTATIVE: Danckers, Andreas M.
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 37 Drawing Figure(s); 34 Drawing Page(s)
LINE COUNT: 2907
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to genetically engineered enzymes, their ligand conjugates, their manufacture, and their use in qualitative or quantitative assays. A hybrid enzyme, such as an AP-epitope, has a foreign amino acid moiety (an epitope) inserted near the active site of the starting AP enzyme. The foreign amino acid moiety binds with an analyte, and, as a consequence of this binding, the enzymatic activity of the hybrid enzyme, AP-epitope, is modified. The changes in the enzymatic activity are dependent upon the presence, or the amount, of the analyte. In another embodiment, the hybrid enzyme consists of a cysteine introduced near the active site of an AP to give a hybrid enzyme. The cysteine on the hybrid enzyme serves as a point of conjugation of a ligand, such as theophylline, ferritin, thyroxine, or digoxigenin, to form the hybrid enzyme-ligand conjugate. The ligand binds with an antibody, an analyte or a binding molecule to an analyte and as a result of this binding, the enzymatic activity of the hybrid enzyme-ligand conjugate is modified or modulated.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 68 OF 71 USPATFULL on STN
ACCESSION NUMBER: 1998:108221 USPATFULL <<LOGINID::20080318>>
TITLE: Devices and methods for detecting multiple analytes in samples
INVENTOR(S): Muller, Uwe Richard, Plano, IL, United States

Lane, David J., Wheaton, IL, United States
PATENT ASSIGNEE(S): Vysis, Inc., Downers Grove, IL, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5804384		19980908
APPLICATION INFO.:	US 1996-761131		19961206 (8)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Sisson, Bradley L.
LEGAL REPRESENTATIVE: Galloway, Norval B.
NUMBER OF CLAIMS: 30
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 7 Drawing Figure(s); 5 Drawing Page(s)
LINE COUNT: 1261
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention features devices that each consist of a tube containing a linear array of specific binding elements that each have capture probes specific for a target analyte linked thereto. The devices of the invention can be used in methods for detecting target analytes in samples.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 69 OF 71 USPATFULL on STN
ACCESSION NUMBER: 97:70867 USPATFULL <<LOGINID::20080318>>
TITLE: Identification of mycobacterium tuberculosis complex species
INVENTOR(S): Jurgensen, Stewart, Raleigh, NC, United States
Little, Michael C., Raleigh, NC, United States
Hamilton, Paul T., Cary, NC, United States
Riska, Paul, Bronx, NY, United States
Chan, John, Yonkers, NY, United States
Bloom, Barry R., Hasting on Hudson, NY, United States
PATENT ASSIGNEE(S): Albert Einstein College of Medicine, a Division of Yeshiva University, Bronx, NY, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5656424		19970812
APPLICATION INFO.:	US 1995-388916		19950215 (8)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Robinson, Douglas W.
ASSISTANT EXAMINER: Wai, Thanda
NUMBER OF CLAIMS: 30
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT: 766
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Methods for using reporter mycobacteriophage (RM) and p-nitro-α-acetylamino-β-hydroxy-propiophenone (NAP) to identify TB complex mycobacteria and distinguish these species from MOTT. RM-infected MOTT show little or no reduction in signal when treated with NAP. In contrast, TB complex mycobacteria infected with RM are distinguishable from RM-infected MOTT by a reduction in signal with NAP treatment.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 70 OF 71 USPATFULL on STN
ACCESSION NUMBER: 97:68037 USPATFULL <<LOGINID::20080318>>
TITLE: Methods of analysis/separation
INVENTOR(S): Parton, Adrian, 6 Swan Grove, Exning, Suffolk CB8 7HX, United Kingdom
Huang, Ying, P.O. Box 89, Houston, TX, United States 77030
Wang, Xiao-Bo, P.O. Box 89, Houston, TX, United States 77030
Pethig, Ronald, Lleyn, Telford Road, Mania Bridge, Gwynedd LL59 5DT, United Kingdom
MacGregor, Alastair R., Field House, Thriplow Road, Fowlmere, Royston, Hertfordshire SG8 70T, United Kingdom
Pollard-Knight, Denise V., 20 Highfield Hall, Highfield Lane, St. Albans AL4 ORL, United Kingdom

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5653859		19970805	
	WO 9416821		19940804	
APPLICATION INFO.:	US 1995-495447		19951120	(8)
	WO 1994-GB121		19940121	
			19951120	PCT 371 date
			19951120	PCT 102(e) date

	NUMBER	DATE
PRIORITY INFORMATION:	GB 1993-1122	19930121

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Gorgos, Kathryn L.
ASSISTANT EXAMINER: Starsiak, Jr., John S.
LEGAL REPRESENTATIVE: Cushman, Darby & Cushman IP Group of Pillsbury Madison & Sutro LLP
NUMBER OF CLAIMS: 14
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 16 Drawing Figure(s); 9 Drawing Page(s)
LINE COUNT: 904
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Particles are subjected to travelling wave field migration (TWFM) to migrate the particles over an array of microelectrodes. Altered particles are produced by treating original particles in such a way so as to alter their TWFM characteristics and the altered TWFM characteristics are employed for analysis and/or separation of the altered particles. The particles may be cells, bacteria, viruses, biomolecules or plastics microspheres. They may be altered by binding to a ligand such as a metal microparticle via a selective linking moiety such as an antibody/antigen or oligonucleic acid, or be physical or chemical treatments.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 71 OF 71 USPATFULL on STN
ACCESSION NUMBER: 87:58546 USPATFULL <<LOGINID::20080318>>
TITLE: Visualization polymers and their application to diagnostic medicine
INVENTOR(S): Ward, David C., Guilford, CT, United States
Leary, Jeffry J., East Haven, CT, United States
Brigati, David J., Hershey, PA, United States

PATENT ASSIGNEE(S): Yale University, New Haven, CT, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4687732		19870818	
APPLICATION INFO.:	US 1983-503298		19830610	(6)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Marantz, Sidney
LEGAL REPRESENTATIVE: Haley, Jr., James F.
NUMBER OF CLAIMS: 45
EXEMPLARY CLAIM: 23
NUMBER OF DRAWINGS: 7 Drawing Figure(s); 5 Drawing Page(s)
LINE COUNT: 1973
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method for detecting a minute quantity of an inorganic or organic target molecule by combining it with a composition of a detecting agent for the target molecule which carries, by direct or indirect means, a visualization polymer. The visualization polymer is composed of multiple units of a visualization monomer which are covalently linked together directly or indirectly covalently linked together by coupling agents which bond to chemical groups of the monomer. The monomer may be an enzyme, a tagged polypeptide, a tagged polyol, a tagged polyolefin or a tagged carbohydrate. The detecting agent may be an antibody, an enzyme, a lectin, strand of a DNA receptor protein, avidin, streptavidin and the like. The visualization polymer produces a high degree of amplification for the detection of the target molecule.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.